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PULMONARY DISEASES: 5,816 CASES IN CHILDREN

WITH SPECIAL REFERENCE TO THE CHILDHOOD TYPE OF PULMONARY TUBERCULOSIS *

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As defined by the American Sanatorium Association at its meeting in Atlantic City, May 27, 1929, the term childhood type of tuberculosis is used to designate the diffuse and focal lesions in the lungs and adjacent tracheobronchial nodes that result from the first infection of the pulmonary tissue by the tubercle bacillus. At the Lymanhurst School for Tuberculous Children in Minneapolis, where about 8,000 children have been examined to date, an unusual opportunity is afforded to study this condition on a rather extensive scale. This report is based on a survey of 5,816 Lymanhurst cases, (tables 1 and 2) in which 3,981 (68.4 per cent) children gave a negative reaction to the Pirquet test, while 1,835 (31.6 per cent) gave a positive reaction to the tuberculin test.

The investigation to which each child was submitted included a complete physical examination, stereoscopic films of the lungs, Pirquet tests and determinations of vital lung capacity, together with a record of the body weight and temperature. In practically all instances, the aforementioned examinations and tests have been repeated for each child several times, thereby making the data rather thorough, complete and reliable. The roentgenologic interpretations were made carefully by Dr. J. R. McNutt, roentgenologist at Lymanhurst, who, after several years of experience, reread all the plates taken in each case included in this study, and his final recapitulatory reading made after this extensive experience was accepted. In many instances the roentgen studies included a series of from eight to ten or more films of the individual subject. This rechecking of the interpretations of the roentgenograms considerably decreased the frequency with which slight glandular calcifications are customarily reported and probably accomplished the nearest approach at present attainable with respect to the correct roentgenologic diag-

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nosis as to the presence or absence of calcium. In addition, this restudy of all the single and serial plates undoubtedly increased the reliability of the interpretations with respect to the presence or absence of various other types of lesions.

Although this survey was undertaken primarily as a study of the childhood type of pulmonary tuberculosis, certain observations are included with reference to the adult type of tuberculosis and to certain nontuberculous lesions. In general, the only observations not reported in this study were limited to findings such as increased branchovascular markings and slight or questionable enlargement of hilus lymph nodes without evidence of calcification.

TABLE 1.—*Percentage (and Actual Number in Parenthesis) of Patients Showing Pathologic and Those Showing Normal Films of the Chest and the Percentage of the Various Types of Disease Roentgenologically Demonstrable in the Entire Group and Also in the Groups with Negative and with Positive Pirquet Tests*

Roentgen Examination	Entire Group (5,816 Children) per Cent	Negative Pirquet Test Cases (3,981 Children) per Cent	Positive Pirquet Test Cases (1,835 Children) per Cent
Pulmonary disease	20.3 (1,179)	6.4 (255)	50.4 (924)
Childhood tuberculosis: all glandular calcifications, Ghon tubercules; resolving parenchymal lesions combined	16.7 (970)	3.9 (154)	44.5 (816)
Childhood tuberculosis (questionable and slight calcifications excluded)	8.5 (493)	0.58 (23)	25.9 (475)
Lesions not belonging to the childhood type of tuberculosis	3.6 (209)	2.5 (101)	5.9 (108)
Calcified hilus glands	10.4 (607)	3.4 (136)	25.7 (471)

In table 2, the data (sexes combined) are grouped in such a manner as to separate those with a negative tuberculin test from those with a positive test. Among the 3,981 children with negative Pirquet reactions, the Mantoux test, with 0.1 mg. of old tuberculin, was given to 368, of whom 33 reacted positive. The group in which the Pirquet test is negative therefore includes certain subjects who had been infected previously by the tubercle bacillus, as demonstrated by this limited application of the Mantoux test. On the basis of the aforementioned findings, one might estimate that the 3,981 children whose Pirquet test was negative probably included about 350 with a positive Mantoux test. This estimate may be excessively high, owing to the fact that the Mantoux test was often used in instances in which special indications for its application were found. The advisability of using the Mantoux rather than the Pirquet test to determine past infection with the tubercle bacillus is recognized, and in the near future it may be possible to report a similar survey of a large group of Lymanhurst children on whom Mantoux tests, with various dosages, have been employed.

GENERAL CONSIDERATIONS

Entire Group.—From the data presented in table 1, it may be seen that intrathoracic disease was revealed by roentgen examination in 1,179, or 20.3 per cent, of the entire group of 5,816 children studied. The most common type of lesions discovered were those representative of the childhood type of tuberculosis (all intrathoracic glandular calcifications, Ghon tubercles and resolving parenchymal lesions combined), which were reported in 16.7 per cent of the total series of cases. In 970 (82.3 per cent) of the 1,179 children in whom disease was demonstrable by roentgen films taken of the chest, lesions of the childhood type of tuberculosis were found. For this sample of the child population of Minneapolis, therefore, the prevailing type of intrathoracic lesion revealed by roentgenograms was that resulting from the first infection by Mycobacterium tuberculosis, which occurred fully four times as frequently as all other types of lesions combined. Since a pathologic condition was discovered in the children with a negative Pirquet reaction as well as in those giving a positive reaction, a consideration of the two groups separated with respect to the reaction to tuberculin seems advisable.

Group with Negative Pirquet Test.—For the 3,981 children showing a negative Pirquet reaction, a pathologic intrathoracic condition was reported in only 255 (6.4 per cent of the cases, table 1). Among the 3,981 children lesions characteristic of the childhood type of tuberculosis were found in 154, or approximately 3.9 per cent. Lesions of this type, although showing a relatively low incidence (3.9 per cent) among the group with a negative tuberculin test, nevertheless constituted fully 60 per cent of all disease demonstrable roentgenologically in this group. The discovery of childhood tuberculosis in children in whom its presence probably was not expected may have been due either to a failure of the Pirquet test to reveal all cases in which infection by the tubercle bacillus had occurred in the past or to error on the part of the roentgenologist in the identification of calcium deposits. Which of these two factors was mainly responsible for these apparent discrepancies is uncertain. The fact that from a limited application of the Mantoux test certain children with positive reactions to tuberculin were known to have been included in the groups in which the Pirquet test was negative makes it reasonable to suspect the presence of demonstrable childhood tuberculous lesions in a certain percentage of the children showing a negative Pirquet test. In the small number of instances in which the Mantoux test was applied, however, the films taken of the chest were found to be normal.

If questionable and slight intrathoracic glandular calcifications are excluded, the childhood type of tuberculous lesions, which may be

identified by the experienced roentgenologist with great reliability, were reported in only 23 (0.58 per cent; table 1) of the children whose Pirquet test was negative. Therefore, the conclusion seems justified that the more conspicuous and thus the more readily recognized lesions characteristic of childhood tuberculosis are rarely discovered by films of the chest in children having a negative Pirquet test.

The general annual increase in all types of intrathoracic disease demonstrable by x-ray films in children with negative Pirquet tests is represented by curve *A* in figure 1, which shows a slow and gradual increase reaching a maximum of about 11 per cent at 13 years of age; the average for all ages combined amounted to 6.4 per cent.

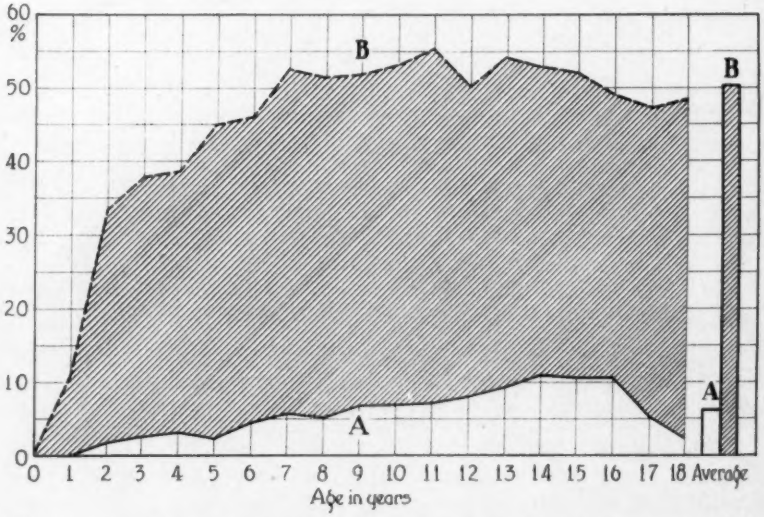

Fig. 1.—Percentage of cases in which pulmonary disease was demonstrable at each year of age and the average for all ages combined. *A* indicates the group of 3,981 children in whom the Pirquet test was negative; *B*, the group of 1,835 children in whom it was positive.

Group with Positive Pirquet Test.—The upper curve, *B*, in figure 1 represents the annual increase in disease reported by the roentgenologist for the children with positive tuberculin tests. The curve shows a rapid increase during the first few years of life in lesions demonstrable by films taken of the chest, reaching a maximum of 55 per cent of the children in the tenth year of life. The shaded zone between the two curves shown in the figure strikingly illustrates the tremendous increase in intrathoracic disease as revealed by the roentgenogram in the group with positive Pirquet tests, owing apparently to the infection by the tubercle bacillus which these children had experienced in the past.

Intrathoracic lesions representative of the childhood type of tuberculosis were revealed by roentgen examination in 44.5 per cent (816

cases, table 1) of the 1,835 children with positive tuberculin reactions, thus greatly exceeding the percentage frequency (5.9) of the combined occurrence of all other types of lesions discovered in this group of cases. When questionable and slight intrathoracic glandular calcifications are excluded, the more conspicuous and readily identified lesions typical of tuberculosis of first infection are still found to exceed any other type of disease found. Thus, resolving parenchymal tuberculosis, moderate and marked glandular calcifications and Ghon tubercles collectively were discovered on roentgen examination in 475 or 25.9 per cent (table 1) of the 1,835 children who had a positive Pirquet test. In this group of children with a positive tuberculin test, therefore, the first infection by the tubercle bacillus was experienced in sufficient dosage to leave unmistakable permanent intrathoracic scars of primary tuberculosis in over one fourth of the cases. The successful manner in which these 1,835 children have withstood infections by this organism received in sufficient dosage to leave these permanent scars, experiencing hardly a day of illness referable to such infection, is rather impressive. These observations may be interpreted as illustrating either that the first infection by the tubercle bacillus even when fairly massive is rather benign and innocuous, or that children are endowed with excellent natural powers to withstand tuberculous infections. The latter interpretation appeals to me.

A test of the efficiency of the roentgen examination in detecting childhood tuberculosis probably is found in the results obtained from the study of the children whose tuberculin reaction was positive, all of whom were known to harbor a focus of tuberculous disease within their bodies, located (as indicated by postmortem findings of Ghon [1] and Opie [2]) in the thorax in from 90 to 95 per cent of the cases. In my series of cases, the roentgenograms revealed unmistakable evidence of the first infection by the tubercle bacillus in slightly more than 25 per cent of the cases, but failed to show unquestioned lesions resulting from this infection in the majority (74 per cent) of cases. In certain instances in this survey, extrathoracic tuberculous lesions were demonstrated; nevertheless, in a large percentage of the infected children included in this study who were known to harbor a tuberculous lesion within their bodies, and, no doubt, often within the thorax, the discovery and identification of this focus by means of the x-ray was impossible. If one tries to evaluate the efficiency of the tuberculin test, the roentgenogram and the stethoscope in making a diagnosis of childhood

1. Ghon, A.: Der primäre Lungenherd bei der Tuberkulose des Kindesalter, Vienna, Urban & Schwartzenberg, 1912.

2. Opie, E. L.: The Focal Pulmonary Tuberculosis of Children and Adults, J. Exper. Med. **25**:855, 1917.

tuberculosis, and assigns an arbitrary value of 100 per cent to the tuberculin (Pirquet) test, on this basis the roentgenogram has a value of about 25 per cent and the stethoscope (as judged by experience) a small fraction of 1 per cent. The tuberculin test, therefore, stands preeminent among the various methods at present available in making a diagnosis of the presence or absence of primary tuberculosis, but gives no information with regard to the location and extent of the diseased area or the presence or absence of adult tuberculosis. Roentgen examination is of inestimable value in that it alone permits one to discover the site, extent and progress of the primary tuberculous lesion when it is situated favorably and is of sufficient size to permit its identification on the roentgenogram. Physical examination is rather profitless and permits discovery of only certain of the more extensive resolving parenchymal lesions of first infection.

Negative Roentgenologic Reports.—The percentage of negative roentgenograms for the group of children not infected by the tubercle bacillus decreased gradually with advancing age, reaching an average minimum of 89 per cent (table 2) about the thirteenth year. For the children whose Pirquet test was positive the percentage of negative roentgenograms taken of the chest likewise shows a decrease with increasing age, reaching a minimum of about 45 per cent around the tenth year. The decline in the percentage of children with films showing a normal chest, however, occurs much more rapidly in the infected than in the noninfected group.

CHILDHOOD TYPE OF PULMONARY TUBERCULOSIS OF PRIMARY INFECTION

Resolving Parenchymal Type of Childhood Pulmonary Tuberculosis (Epituberculosis?).—The diagnosis of resolving parenchymal tuberculous lesions was based on repeated roentgen examinations which revealed parenchymal lesions in children with positive tuberculin tests which persisted for weeks and months, but which eventually disappeared with the subsequent deposit of calcium in the adjacent hilus glands or the development of Ghon tubercles and calcified hilus glands. On initial examination the roentgenologic study usually does not justify or permit an identification of the lesion as being tuberculous in origin, since simple nontuberculous pneumonic consolidations may present similar shadows on the x-ray film. However, in children with positive tuberculin tests presenting no clinical symptoms of pneumonia, the roentgenologic demonstration of pneumonic-appearing lesions which slowly resolve with the subsequent appearance of calcium deposits in the adjacent lymph nodes, with or without the development of a Ghon tubercle, a diagnosis of a resolving parenchymal tuberculous lesion of

TABLE 2.—*Number of Children and Number and Percentage of Cases in Which Various Types of Intrathoracic Lesions Were Found by Roentgen Examination*

TABLE 2.—*Number of Children and Number and Percentage of Cases in Which Various Types of Intrathoracic Lesions Were Found by Roentgen Examination for Each Age Group in Children with a Negative Pirquet Test and with a Positive Pirquet Test*

Age	No. of Children	Mantoux Tests		Negative Roentgen Examinations		Childhood Type of Tuberculosis										Adult Type of Tuberculosis		Questionable Tuberculosis				Nontuberculous Lesions					
						Resolving Parenchymal Lesions		Intrathoracic Glandular Calcifications						Ghon Tubercles				Pleural Thickening		Pleural Effusion		Bronchiectasis		Pneumonia		Pneumothorax	
								Questionable		Slight		Moderate		Marked													
		No. Positive	No. Negative	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Children with a Negative Pirquet Test																											
0-11 mo.	107	0	4	107	100	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...
1 yr.	115	1	3	113	98.3	..	...	..	...	1	0.9	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...
2 yr.	153	0	5	149	97.4	..	...	..	...	2	1.3	..	...	..	...	..	...	2	1.3	..	...	..	...	..	...	1	0.9		
3 yr.	183	0	10	177	96.7	..	...	1	0.6	2	1.1	..	...	..	...	..	...	1	0.6	..	...	1	0.6	1	0.6	..	...		
4 yr.	212	0	12	207	97.6	..	...	2	0.9	..	...	..	...	..	...	1	0.5	1	0.5	..	...	..	...	1	0.5	..	...		
5 yr.	242	2	16	231	95.5	..	...	3	1.2	1	0.4	..	...	..	...	..	...	3	1.2	..	...	2	0.8	2	0.8	..	...		
6 yr.	323	1	18	305	94.4	..	...	6	1.8	6	1.8	..	...	..	...	1	0.3	3	0.9	..	...	1	0.3	1	0.3	..	...		
7 yr.	326	1	27	309	94.8	..	...	5	1.5	2	0.6	1	0.3	..	...	1	0.3	5	1.5	..	...	2	0.6	..	...	1	0.3		
8 yr.	337	2	25	314	93.2	..	...	8	2.4	3	0.9	1	0.3	..	...	2	0.6	5	1.5	..	...	3	0.9	1	0.3	..	...		
9 yr.	296	5	25	276	93.6	..	...	4	1.4	7	2.4	..	...	..	...	3	1.0	5	1.7	..	...	1	0.3	..	...	..	...		
10 yr.	312	3	24	290	92.9	..	...	3	1.0	8	2.6	..	...	..	...	2	0.6	2	0.6	4	1.3	..	..	2	0.6	1	0.3	..	...
11 yr.	321	3	34	295	91.9	..	...	2	0.6	12	3.7	1	0.3	..	...	..	...	..	...	11	3.4	..	...	..	...	..	...	..	...
12 yr.	277	6	35	251	90.6	..	...	9	3.3	5	1.8	..	...	..	...	3	1.1	1	0.3	7	2.5	..	...	1	0.3	..	...	..	...
13 yr.	228	1	32	203	89.0	..	...	2	0.9	10	4.4	..	...	..	...	2	0.9	..	...	8	3.5	..	...	3	1.3	..	...	..	...
14 yr.	232	3	28	208	89.7	..	...	7	3.0	8	3.5	..	...	1	0.43	1	0.4	..	...	4	1.7	..	...	..	...	3	1.3	..	...
15 yr.	199	4	25	178	89.4	..	...	6	3.0	4	2.0	..	...	..	...	2	1.0	..	...	5	2.5	1	0.5	2	1.0	1	0.5	..	...
16 yr.	77	0	11	73	94.8	..	...	1	1.3	1	1.3	..	...	..	...	..	...	..	...	..	...	..	...	2	2.6	..	...	..	...
17 yr.	41	1	1	40	97.6	..	...	..	...	..	...	1	2.4	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...
Total and averages	3,981	33	335	3,726	93.59	0	0	59	1.5	72	1.8	4	0.10	1	0.025	18	0.45	3	0.075	64	1.6	1	0.025	20	0.5	11	0.28	2	0 05
Children with a Positive Pirquet Test																											
0-11 mo.	17	0	0	15	88.2	1	5.9	1	5.9	..	....	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...	..	...
1 yr.	27	1	0	18	66.7	6	22.2	..	...	1	3.7	1	3.7	..	...	1	3.7	..	...	..	...	..	...	..	...	..	...	..	...
2 yr.	45	3	0	28	62.2	5	11.1	1	2.2	4	8.9	2	4.4	..	...	5	11.1	..	...	..	...	..	...	..	...	..	...	..	...
3 yr.	44	1	0	27	61.4	8	18.2	..	...	3	6.8	2	4.5	..	...	4	9.1	..	...	..	...	..	...	..	...	..	...	..	...
4 yr.	60	2	0	33	55.0	5	8.3	..	...	8	13.3	3	5.0	..	...	8	13.3	..	...	2	3.3	1	1.7	..	...	..	...	..	...
5 yr.	87	13	0	47	54.0	5	5.7	6	6.9	10	11.5	1	1.1	3	3.4	13	14.9	..	...	1	1.1	..	...	..	...	..	...	1	1.1
6 yr.	105	11	0	47	44.8	5	4.8	6	5.7	18	17.1	4	3.8	1	0.95	17	16.2	1	1.0	4	3.8	1	1.0	1	1.0	..	...	..	...
7 yr.	128	12	0	62	48.4	8	6.3	7	5.5	21	16.4	3	2.3	1	0.8	19	14.8	1	0.8	3	2.3	1	0.8	2	1.6	..	...	..	...
8 yr.	131	13	0	63	48.1	6	4.6	7	5.3	19	14.5	7	5.3	..	...	21	16.0	2	1.5	4	3.0	1	0.8	1	0.8	..	...	..	...
9 yr.	147	26	0	69	46.9	5	3.4	7	4.1	16	10.9	16	10.9	1	0.7	25	17.0	4	2.7	4	2.7	..	...	..	...	..	...	..	...
10 yr.	161	18	0	72	44.7	3	1.9	13	8.1	20	12.4	10	6.2	3	1.9	29	18.0	2	1.2	6	3.7	..	...	3	1.9	..	...	..	...
11 yr.	139	15	0	69	49.6	5	3.6	10	7.2	18	12.9	9	6.5	1	0.7	21	15.1	1	0.7	5	3.6	..	...	..	...	..	...	..	...
12 yr.	166	20	1	76	45.7	2	1.2	12	7.2	31	18.7	14	8.4	1	0.6	22	13.3	3	1.7	4	2.4	1	0.6	..	...	..	...	..	...
13 yr.	151	17	0	71	47.0	..	...	9	6.0	25	16.6	15	9.9	..	...	21	13.9	9	6.0	..	...	1	0.7	..	...	..	...	..	...
14 yr.	151	23	0	72	47.7	1	0.7	6	4.0	19	12.6	6	4.0	2	1.3	28	18.5	7	4.6	8	5.3	..	...	2	1.3	..	...	..	...
15 yr.	150	5	0	76	50.7	..	...	5	3.3	19	12.7	8	5.3	5	3.3	30	20.0	3	2.0	4	2.7	..	...	..	...	..	...	..	...
16 yr.	95	26	0	50	52.6	1	1.1	3	3.1	9	9.5	7	7.4	1	1.1	13	13.7	9	9.5	1	1.1	..	...	1	1.1	..	...	..	...
17 yr.	31	6	0	16	51.6	..	...	1	3.2	6	19.4	3	9.7	..	...	2	6.5	3	9.7	..	...	..	...	..	...	..	...	..	...
Total and averages	1,835	212	1	911	49.6	66	3.6	94	5.1	247	13.5	111	6.0	19	1.0	279	15.2	45	2.5	46	2.5	6	0.33	10	0.54	..	...	1	0.054

first infection is justified. In fact, after careful study a diagnosis often is justified long before calcium deposits appear. This earliest stage characteristic of the first (massive?) infection by the tubercle bacillus constitutes a rather definite and fairly uniform clinical entity. The diffuse parenchymal lesions quite uniformly tend to recede slowly as time elapses, following which intrathoracic glandular calcifications appear. Physical signs are usually inconspicuous even in the presence of rather extensive infiltrations. During the course of the resolution of the parenchymal lesion the child usually has little or no fever, often presents only moderate leukocytosis and continues to eat well and to show a satisfactory gain in weight. The deleterious effects of these lesions on the general health of the child are strikingly absent, even in

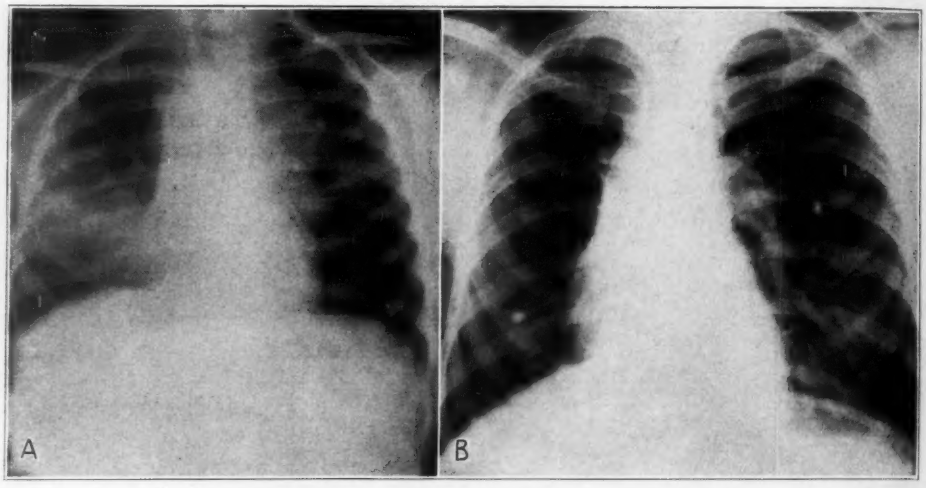

Fig. 2.—*A*, roentgenogram showing a large parenchymal lesion in lower part of right pulmonary field, and a second large lesion extending laterally from the hilus of a child (C. D.) 2 years of age. A diagnosis of resolving parenchymal tuberculosis of first infection was made. *B*, roentgenogram taken when C. D. was 9 years old, showing complete resolution of primary parenchymal tuberculosis and replacement by two Ghon tubercles, the permanent and relatively inconspicuous evidence of the parenchymal lesions that once existed (see fig. 2).

instances of involvement of an entire pulmonary lobe, and stand in marked contrast with the evidence of prostration, toxicity and debility manifested by patients suffering from adult tuberculous lesions of reinfection of similar extent.

The resolving parenchymal lesion produced by the first infection by the tubercle bacillus was the only type of tuberculous lesion found exclusively in the group giving positive reactions to tuberculin. In all, 66 such cases were seen (table 2), which amounted to about 3.6 per cent of the 1,835 children with a positive Pirquet test. With advancing

age, the relative or percentage yearly frequency with which the resolving tuberculous parenchymal lesion was discovered shows an initial rise to 22.2 in the second year of life, but thereafter the frequency tended generally toward a progressive annual decline, and the condition was rarely found after the eleventh year. In spite of the fact that the most extensive of the lesions characteristic of pulmonary tuberculosis of first infection were present with the greatest frequency in the first three or four years of life, and thus in the age period when resistance to tuberculosis has been commonly and possibly erroneously considered to be very poor, these children quite uniformly recovered, if protected from further infection, as was usually possible in this series as a result of the activities of the health department of Minneapolis, instituted by Dr. F. E. Harrington.

The pulmonary lesions found in one of these children at 2 years of age are shown in figure *2A*, at which time an extensive parenchymal shadow was present in the lower field of the right lung and a second large lesion was found extending laterally from the mediastinum in the upper portion of the left lung. As time elapsed these two areas of infiltration gradually subsided, and in 1930, when the patient was 9 years old, two Ghon tubercles were found associated with calcified hilus glands (fig. *2B*), the permanent and now relatively inconspicuous evidence of the extensive parenchymal lesion which once existed. Similarly, in several other cases opportunity was afforded to follow the development of Ghon tubercles at the site of previously existing parenchymal lesions by serial roentgenograms of the chest. In a large number of instances the consolidation disappeared completely, leaving no demonstrable trace of its former existence in the lung tissue, although in such cases calcium deposits later appeared in the regional lymph nodes with great regularity.

Hempelman [3] was among the first to call attention to the fact that the prognosis of tuberculosis in infancy, even when massive and infiltrating, was not necessarily fatal. He cited a large number of cases, in 6 of which the ages ranged from 6 weeks to 1 year, in which clinical health was maintained over a period ranging from fifteen months to five years. Eliasberg and Neuland [4] described resolution in from six to twelve months of extensive parenchymal infiltrations of one or more lobes of the lungs in infants giving a positive reaction to tuberculin. These lesions they termed epituberculosis. They resembled lesions reported by others, however, in tending to resolve and in having a comparatively benign course.

3. Hempelman, T. C.: The Prognosis of Pulmonary Tuberculosis in Infancy, Am. Rev. Tuberc. **1**:99, 1917.

4. Eliasberg, H., and Neuland, W.: Epituberculous Infiltration of the Lung in Children, Jahrb. f. Kinderh. **93**:88, 1920.

Ribadeau-Dumas and Béclère [5] cited an instance of extensive pulmonary involvement in an infant 9 months of age infected by a servant with open pulmonary tuberculosis. At 6 years of age this child was well and strong, and the chest showed no abnormal condition. Eichelberg [6] reported a similar case in a child 13 months of age, in which the roentgenogram revealed a dense shadow over the entire right side of the chest. Eight months later the patient was clinically well, and roentgen examination revealed improvement in the intrathoracic condition. Greenberg [7] reported the recovery of 2 infants in whom extensive parenchymal lesions were discovered at the ages of 12 and 17 months, respectively. Langer [8] observed the complete resolution of an extensive infiltration in a child, which four years later suddenly reappeared for a period of two weeks following the subcutaneous administration of 0.1 mg. of tuberculin. Bernard and Paraf [9] showed films of the chests of 11 infants having resolving parenchymal lesions due to primary tuberculous infections. These infants uniformly did well. Gerstenberger and Burhans [10] reported recovery of 7 infants under 18 months of age from extensive tuberculous infiltration which, in some instances, presented cavitation. Kölzer [11] uses the term epituberculosis for a type of consolidation that is found in tuberculous children, and states that the condition runs a benign course for weeks, causes little fever, and spreads rapidly, usually from the hilus to the periphery, and then resolves slowly from the periphery to the hilus. Whether or not the condition termed epituberculosis by Eliasberg and Neuland, Kölzer, Goldberg and Gasul,[12] and others differs from the parenchymal lesions of primary tuberculous infection is unknown. There is reason to suspect that the term epituberculosis is superfluous, and that lesions to which this term is applied properly belong to the group of resolving tuberculous lesions of first infection of the lung parenchyma. Among others, Stoloff [13] also presented serial x-ray plates showing the resolution of parenchymal lesions and their subsequent replacement by Ghon tubercles.

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5. Ribadeau-Dumas, L., and Béclère, H.: Arch. de méd. d'enf. **23**:728, 1920.
6. Eichelberg: Monatschr. f. Kinderh. **18**:123, 1920.
7. Greenberg, D.: Chronic Tuberculous Hilus Pneumonia in Children, Am. J. Dis. Child. **21**:65 (Jan.) 1921.
8. Langer, H.: Ztschr. f. Kinderh. **34**:142, 1922.
9. Bernard, L., and Paraf, J.: Les formes curables de la tuberculose évolutive du nourrison, Ann. de méd. **19**:638, 1926.
10. Gerstenberger, H. J., and Burhans, C. W.: Treatment of Extensive Pulmonary Tuberculosis with Ultraviolet Rays, Am. J. Dis. Child. **33**:54 (Jan.) 1927.
11. Kölzer, W.: Epituberculous Infiltration, Jahrb. f. Kinderh. **115**:194, 1927.
12. Goldberg, B., and Gasul, B.: Epituberculosis: A Study of Ten Cases for a Period of Over Two Years, Am. J. M. Sc. **180**:824, 1930.
13. Stoloff, E. G.: Primary Infection in Tuberculosis, Am. J. Dis. Child. **33**: 363 (March) 1927.

Kohn [14] reported a case in a child who at 12 weeks of age showed a positive reaction to tuberculin. A parenchymal pulmonary lesion was present in this case. The patient was observed over a period of five years, at which time it was considered to be in perfect health. Beaven [15] reported a case of tuberculosis in an infant with extensive pulmonary involvement which resolved. Aside from the fact that in this instance an unusual type of tubercle bacillus was isolated, Beaven's case resembled that seen by others in which the human strain of organism was the probable causative agent. The cases reported in this survey, together with those reported by various other authors apparently establish the fact that in infancy especially when an initial infection of the lung by the tubercle bacillus occurs, an extensive and often relatively benign lesion frequently develops, which characteristically tends to resolve slowly, and which may be appropriately designated as resolving parenchymal pulmonary tuberculosis of first infection.

INTRATHORACIC GLANDULAR CALCIFICATIONS

Questionable Calcification.—Questionable calcification of the intrathoracic lymph nodes was reported in 59 or 1.5 per cent of the 3,981 children with a negative Pirquet test (table 2) and in 94 or 5.1 per cent of the 1,835 cases in which the tuberculin test was positive. These minute traces of calcium which are often difficult to differentiate from shadows appearing on films of the chest owing to varying densities in intrapulmonary structure, were reported by the roentgenologist relatively 3.4 times as frequently in children having a positive tuberculin reaction as in those having a negative one. The relative frequency of the occurrence of questionable calcification at different ages (table 2) presented no uniform trend with increasing age, aside from the fact that this lesion was reported more frequently in the older than in the younger groups of children, as previously mentioned. However, attention is called to the more frequent occurrence of questionable calcification in the children with a positive reaction than in those with a negative one.

Slight Calcification.—Slight calcification of the glands at the root of the lungs was reported in 1.8 per cent, 72 cases (table 2), of the children with a negative reaction to tuberculin and in 13.5 per cent, 247 cases, of those with a positive one. This type of lesion, therefore, was reported relatively 7.5 times as frequently for children with a positive reaction to the tuberculin test as for those reacting negatively to the Pirquet test. With advancing age the percentage of cases show-

14. Kohn, J. L.: Tuberculous Infection of the Lung in Early Infancy, Am. Rev. Tuberc. **17**:565, 1928.

15. Beaven, P. W.: Infantile Pulmonary Tuberculosis Due to an Unusual Type of Tubercle Bacillus, Am. J. Dis. Child. **39**:1270 (June) 1930.

ing slight calcification of lymph nodes within the thorax tends to increase, the increase occurring more rapidly in the group in which the Pirquet test was positive than in the group in which it was negative. The data are insufficient, however, to identify any definite details of this trend at different ages. For the 1,835 children having a positive Pirquet test, slight calcification was reported relatively 2.6 times as frequently as questionable calcification (13.5 and 5.1 per cent, respectively).

Questionable and slight calcifications of intrathoracic lymph nodes often are reported by roentgenologists with such monotonous regularity for children with a negative tuberculin reaction as well as for those with a positive reaction that one may well be generally skeptical as to the accuracy of the identification of small calcium deposits in many instances. The data presented in this survey indicate, however, that when such identifications are made carefully and are based on evidence of reasonable certainty, these inconspicuous calcium deposits are reported more frequently in children in whom their presence is to be expected (in those who react positively to tuberculin) than in cases in which they are not expected to be present (in uninfected children). That questionable and slight glandular calcifications were reported in an appreciable number of children who reacted negatively to the Pirquet test probably is not surprising if one considers that in these instances the roentgenologist is attempting to recognize small calcium deposits that may be easily confused with shadows produced by intrapulmonary vessels situated at right angles to the plane of the x-ray film, or with shadows resulting from the summation of superimposed structural densities present within the lungs.

Moderate Calcification of the Intrathoracic Lymph Nodes.—Moderate degrees of calcification of the lymph nodes at the root of the lungs were rarely reported, in 4 cases (table 2) in the 3,981 children with a negative Pirquet test, which for these cases represents an incidence of only 0.1 per cent, as compared with an incidence of 6 per cent (111 cases) for the group with positive reaction to tuberculin. Examples of this type of lesion, therefore, were found relatively sixty times as frequently among the infected as among the uninfected children. Thus in cases showing a moderate degree of glandular calcification, a lesion that can be identified by the roentgenologist with great certainty, the data reveal this type of lesion to be reported almost exclusively in persons having a positive reaction to tuberculin. It was indeed exceptional to encounter moderate calcification of the intrathoracic lymph nodes in persons with a negative Pirquet test, and in a certain per cent, if not in the majority of such discrepancies, the application of the Mantoux test probably will give unmistakable evidence of a past infection by the tubercle bacillus.

A committee consisting of Pancoast, Dunham and Baetjer,[16] appointed by the National Tuberculosis Association for the express purpose of studying the roentgenologic findings in the chests of normal children, concluded that calcified nodes at the root of the lung, without evidence of pulmonary disease, are of no significance except as a possible evidence of some healed inflammatory condition possibly, but not necessarily, tuberculous. From this study of the Lymanhurst cases, I have reached the conclusion that reports by a competent roentgenologist of questionable and slight calcification of the hilus glands often indicate the discovery of small quiescent tuberculous lesions, and that the identification of rather conspicuous intrathoracic calcium deposits establishes with great certainty the presence of tuberculosis at the site of calcification. The reliability with which childhood tuberculosis involving the intrathoracic lymph nodes may be diagnosed from the film of the chest is proportional in a measure to the degree of calcification demonstrable in these nodes.

In the group with a positive Pirquet test, moderate calcifications were found slightly more frequently than questionable calcifications, and about one-half as often relatively as the slight degree of calcification. With advancing age the relative frequency of the occurrence of moderate calcification of the intrathoracic glands shows considerable yearly irregularity, tending to appear less frequently before the eighth year than later.

Marked Calcification of the Intrathoracic Nodes.—Marked calcification of the hilus and paratracheal lymph nodes was found less often relatively than the other degrees of calcification previously mentioned in both the group in which the tuberculin test was negative and that in which it was positive, being reported in only 0.025 and 1.04 per cent (table 2) of each group, respectively. This type of lesion, however, was found relatively over forty-one times as frequently in the positive as in the negative cases.

Among the children with a positive tuberculin test, marked calcifications were not seen until the fifth year of life, and thereafter they occurred relatively so irregularly that no definite trend with increasing age could be detected.

A general consideration of the data for all degrees of calcification of the hilus and paratracheal lymph nodes reveals that the combined total for lesions of these types (607 cases, table 1) amounted to 10.4 per cent of the entire group of 5,816 children. When the two groups are separated with respect to their reaction to tuberculin, the totals for the various degrees of intrathoracic calcification amounted to 3.4 per

16. Pancoast, H. K.; Dunham, K., and Baetjer, F. H.: Clinical and X-Ray Findings in the Chest of Normal Children, Am. Rev. Tuberc. **6**:331, 1922.

cent (136 cases) for the 3,981 children with a negative reaction to tuberculin as compared with 25.7 per cent (471 cases) for the 1,835 children with a positive Pirquet test. The percentage of intrathoracic glandular calcifications on the whole, disregarding the degree of calcium, therefore, was reported approximately 7.5 times in the group in which the Pirquet test was positive to once in the group in which it was negative. This observation illustrates that the previous infection by the tubercle bacillus, which has been experienced by the former group, has left definitely demonstrable lesions in the intrathoracic lymph nodes in an appreciable number (25.7 per cent) of such cases.

GHON TUBERCLES

Ghon tubercles were found in 5.1 per cent (297 cases, table 2) of the entire group of 5,816 children examined. A certain number of these (18 cases) were reported among the children with a negative Pirquet test, a relative incidence of 0.45 per cent. The remaining 279 Ghon tubercles occurred in the cases in which the Pirquet test was positive, amounting to an approximate average of 15.2 per cent of the number of persons included in this group. The relative occurrence of Ghon tubercles in the group with a positive tuberculin test, therefore, was more than thirty-three times as frequent as in the group with a negative test. In practically every instance in which a Ghon tubercle was demonstrable, calcification was also present in the hilus lymph nodes, occurring particularly homolaterally with respect to the position of the Ghon tubercle. In certain cases these tubercles were multiple, and in instances in which they were located in both pulmonary fields, the hilus glands usually presented evidence of bilateral calcification. The degree of intrathoracic glandular calcification accompanying Ghon tubercles varied from questionable to marked, with the moderate and marked degrees of calcification predominating. In instances in which it was possible to observe children having this type of lesion over a period of a few years, a general tendency for the glandular calcium deposits to increase slowly in amount was noted, whereas the condition of the Ghon tubercle, when once well defined, remained practically unchanged for years. Except for calcification of the intrathoracic lymph nodes, the Ghon tubercles constituted relatively the most frequent single lesion belonging to the childhood or first infection type of tuberculous pulmonary lesions found in the group in which the tuberculin reaction was positive. With advancing age the relative frequency of the occurrence of Ghon tubercles (table 2) shows no distinct trend in either group of children studied, aside from their comparative scarcity in the first year or so of life. A consideration of all cases showing lesions of the childhood type of tuberculosis (intrathoracic glandular calcifications, Ghon tubercles and resolving parenchymal lesions) reveals that of the

1,835 infected children, this general type of pathologic process was reported by the roentgenologist in 816 instances, or in approximately 44.5 per cent of the group (table 1). On the basis of these findings it therefore appears that by careful and thorough studies the roentgen rays demonstrate lesions typical of childhood tuberculosis in almost half of the cases examined, and fail to reveal it in the remaining cases, in which the presence of an intrathoracic lesion is probable. As previously mentioned, if questionable and slight calcifications are excluded, roentgen evidence of childhood tuberculosis is found in only one fourth of the infected children. The tuberculin test, therefore, is definitely superior to roentgen examination, so far as a diagnosis of the first infection by the tubercle bacillus is concerned.

ADULT TYPE OF TUBERCULOSIS

Examples of the adult type of pulmonary tuberculosis were reported in the group in which the Pirquet test was negative and in the group in which it was positive. In the former group, 3 cases of this type (table 2) were found, which amounted to 0.075 per cent of these children. Among the children with a positive Pirquet test 45 (2.5 per cent) were discovered to have adult pulmonary tuberculosis. Therefore the data indicate that this type of lesion occurred relatively about thirty-two times as frequently in the group with positive reactions to tuberculin as in that with negative reactions. Adult pulmonary tuberculosis was not found in the infected children until the sixth year of life (table 2), and thereafter it occurred in relatively small and irregular percentages of the various age groups until about the time of puberty, at which period a rather abrupt rise in its incidence was noted.

In this group of children unmistakable evidence was discovered of the recent development of lesions of the adult type superimposed on and postdating previously existing and nonprogressive scars of childhood or first infection tuberculous pulmonary disease. These adult lesions usually were apical or subapical; as a rule, they did not coincide with the site of the primary tuberculous focus, and tended to develop in the opposite, as well as in the same, lung as that in which the primary focus was located. For example, one child was known to react positively to tuberculin in 1928, and at this time calcification of a gland in the left hilus region was discovered (fig. 3*A*). Two years later, when the girl was 13 years of age, a parenchymal lesion developed in the left subapical region (fig. 3*B*), which, after remaining stationary in extent for seven months, began to spread rapidly and progressed to a fatal termination in a period of four months, in spite of prompt hospitalization, and the employment of phrenicotomy, pneumothorax and general

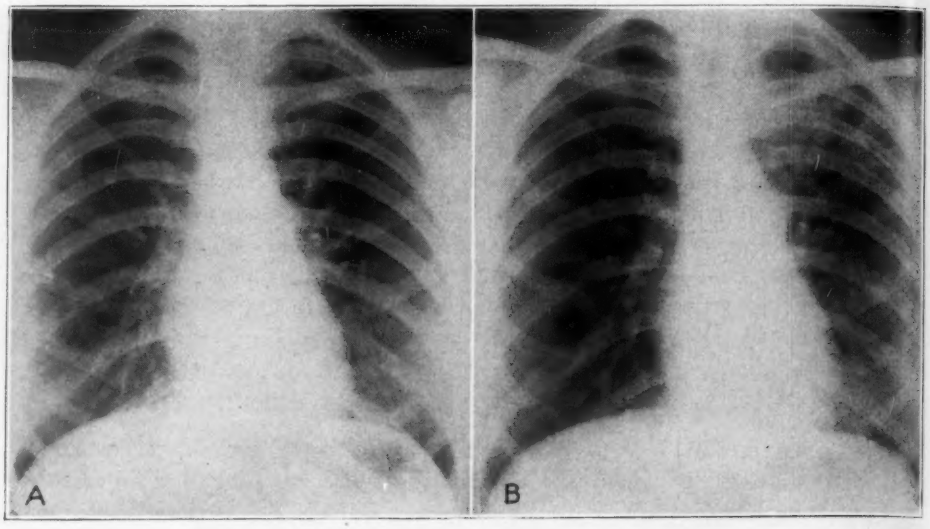

Fig. 3 *A*, roentgenogram showing childhood type of tuberculosis represented by a calcified gland in the left hilar region of a girl (M. S.) 11 years of age; *B* shows the development two years later of the adult type of tuberculosis in the left subapical region in this girl (M. S.), postdating the childhood type of lesion of primary tuberculosis. Death occurred eleven months later.

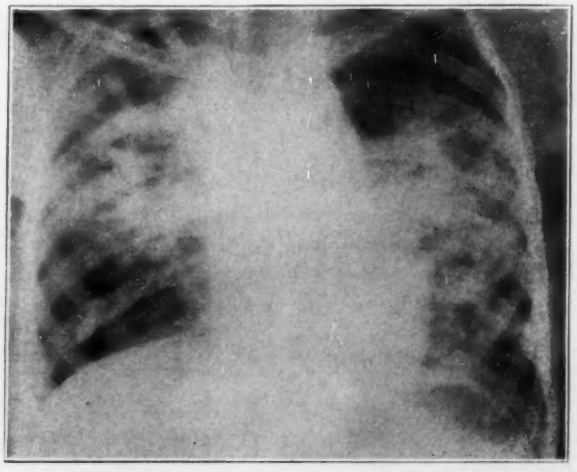

Fig. 4.—X-ray film showing extensive bilateral adult type of pulmonary tuberculosis in a girl (C. E.) 15 years of age. Note the old calcified quiescent Ghon tubercle at the right base, the remaining scar of the primary or childhood tuberculosis which was followed by the adult type of lesion.

remedial and supportive measures. In another instance an extensive bilateral adult pulmonary tuberculosis was discovered, and in this case a large Ghon tubercle was seen in the basal portion of the right lung (fig. 4). Other examples, similar to those cited, were also noted, although in this survey no effort was made to study the frequency of the occurrence of the adult pulmonary tuberculosis postdating and superimposed on the old childhood type of lesion. From a study of this subject, Rathbun [17] concluded that in one half of the cases of pulmonary tuberculosis found in high school and junior high school students, there are signs of latent childhood tuberculosis. He estimated that 75 per cent of the potential cases of pulmonary tuberculosis that will develop in children in the teens occur in a group of children with childhood tuberculosis, their brothers and sisters and other known contacts without demonstrable disease.

Myers and Kernkamp [18] found unquestionable evidence of coexisting adult and childhood tuberculosis in 42.5 per cent of 165 cases studied in the teens. The data of Rathbun and of Myers and Kernkamp, which indicate that 50 per cent or more of cases of the adult and fatal type of tuberculosis develop in persons who have had a childhood lesion at some earlier date, suggest that the immunity against tuberculosis, which is alleged to result from this primary childhood type of first infection, is by no means notoriously effective in preventing reinfections from producing the subsequent development of a form of the disease which proves to be far more serious than that which resulted from first infection. The truth of the situation in such cases may be as follows: The fact that a child has once been infected prevents him from subsequently reacting to later infections as he did following the initial contact with the tubercle bacillus, and consequently, on account of this altering of the natural immunity with which he was initially endowed, he is doomed on reinfection to pass through all the vicissitudes characteristic of adult tuberculosis.

QUESTIONABLE TUBERCULOUS LESIONS

Pleural Thickening and Effusion.—Pleural thickening was found in 1.6 per cent (64 cases, table 2) of the group with a negative Pirquet test as compared with an incidence of 2.5 per cent (46 cases) of the group with a positive test. The data indicate, therefore, that the first infection by the tubercle bacillus and the subsequent development of

17. Rathbun, W.: Epidemiological Basis for the Control of Tuberculosis Among Children, Tr. Nat. Tuber. A., 1929.

18. Myers, J. A., and Kernkamp, L. M.: Tuberculosis Among Girls and Boys in Their Teens, Am. Rev. Tuberc. **21**:509, 1930.

the childhood type of lesion caused an appreciable relative increase in thickening of the pleura. However, only in those instances in which the thickening developed either at the site of previously recognized resolving tuberculous parenchymal lesions or adjacent to a Ghon tubercle could the tuberculous origin of the pleural thickening be suspected with any degree of certainty.

Pleural effusions also were found more frequently in the children with a positive Pirquet test than in those with a negative test, the percentage of frequency of the occurrence of this type of lesion amount-

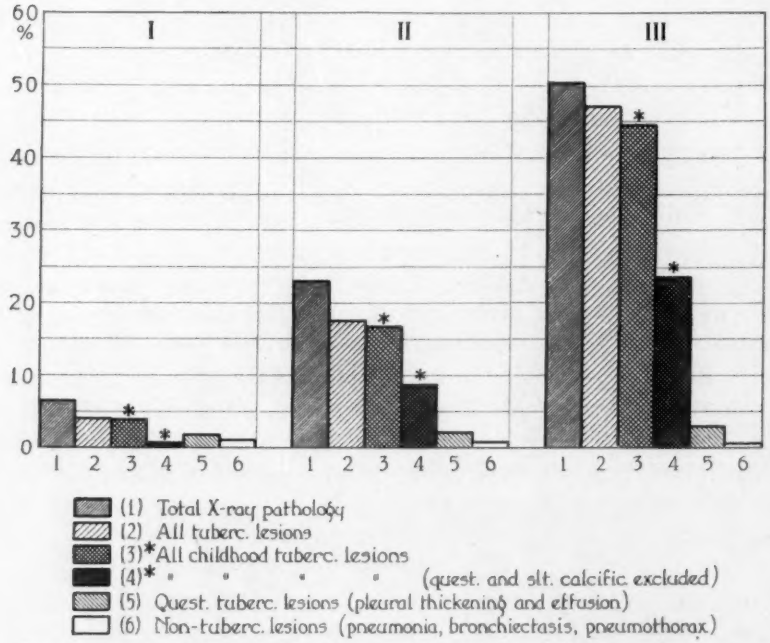

Fig. 5.—Total percentage of roentgenologic reports of disease and percentage of general types of disease. *I* represents group of 3,981 children in whom the Pirquet test was negative; *II*, 5,816 children (groups I and II combined) and *III*, 1,835 children in whom it was positive.

ing to 0.33 and 0.025 per cent for each group, respectively (table 2). In general, the data seem to indicate that pleural thickenings and effusions are relatively uncommon complications following the development of childhood tuberculosis.

Nontuberculous Lesions: Bronchiectasis, Pneumonia and Pneumothorax.—These three conditions were found in a comparatively small percentage of the group as a whole, and, as was probably to be expected, bronchiectasis and pneumothorax occurred in practically an equal percentage in the cases with a positive tuberculin test and in those with a

negative test. With respect to pneumonia, the occurrence of this lesion exclusively in the group with a negative Pirquet test was possibly accidental. At any rate, an infection by the tubercle bacillus during childhood was not followed by an increased incidence of bronchiectasis, pneumonia or pneumothorax in this group.

A clear conception of the relative frequency of the occurrence of various general types of lesions (childhood tuberculosis, questionable tuberculous lesions and nontuberculous lesions) demonstrated by roentgen examination of the children with a negative Pirquet test and those with a positive test included in this study, may be obtained from inspection of figure 5. The figure probably is self-explanatory; thus a detailed consideration of it is omitted.

PROBABILITY

Throughout this paper the data have been considered with respect to percentage relationships. Another convenient and, at times, desirable method that may be employed in the treatment of data involves the application of the mathematical theorem of probability. For example, one may wish to determine the probability of the Pirquet test being negative or positive in cases showing questionable calcification of the intrathoracic glands by roentgen examination. In this study, a total of 153 children (table 2) was found to have this type of lesion, of which 59 and 94 reacted negatively and positively, respectively, to the Pirquet test. On the basis of these findings, the probability that the Pirquet test is negative for children having questionable glandular calcifications is 59:153 or 0.39. Also for these children the probability that the Pirquet test is positive is 94:153, or 0.61. On the basis of these data, it is also true that among children having questionable calcification of the intrathoracic lymph nodes demonstrable by roentgen examination, 39 and 61 per cent had negative and positive Pirquet reactions, respectively. The numerous other probabilities embodied in the data obtained from this survey are self-evident and need not be particularly enlarged on. Certain of these probabilities are listed.

LIST OF PROBABILITIES

Total number of children	5,816
Total normal on roentgen examination	4,637
Total having disease revealed by roentgen examination	1,179
Total number with negative Pirquet test	3,981
Total number with positive Pirquet test	1,835
Total negative roentgenograms for children with a negative Pirquet test	3,726
Total positive roentgenograms for children with a negative Pirquet test	255
Total negative roentgenograms for children with a positive Pirquet test	911
Total positive roentgenograms for children with a positive Pirquet test	924

For Group as a Whole:

Probability that the roentgen examination is negative..... $\frac{4,637}{5,816} = .80$

Probability that the roentgen examination is positive..... $\frac{1,179}{5,816} = .20$

Probability that the Pirquet test is negative..... $\frac{3,981}{5,816} = .68$

Probability that the Pirquet test is positive..... $\frac{1,835}{5,816} = .32$

For Children Having a Negative Pirquet Test:

The probability that the roentgen examination is negative..... $\frac{3,726}{3,981} = .94$

The probability that the roentgen examination is positive..... $\frac{255}{3,981} = .06$

For Children Having a Positive Pirquet Test:

The probability that the roentgen examination is negative..... $\frac{911}{1,835} = .50$

The probability that the roentgen examination is positive..... $\frac{924}{1,835} = .50$

For Children Having Disease Found by Roentgen Examination:

The probability that the Pirquet test is negative..... $\frac{255}{1,179} = .22$

The probability that the Pirquet test is positive..... $\frac{924}{1,179} = .78$

For Children Having a Negative Roentgen Examination:

The probability that the Pirquet test is negative..... $\frac{3,726}{4,637} = .80$

The probability that the Pirquet test is positive..... $\frac{911}{4,637} = .20$

Compound Probabilities (Entire Group):

The compound probability that the results of roentgen examination and Pirquet test are both negative $= .80 \times .68 = .544$.

The compound probability that the results of roentgen examination and Pirquet test are both positive $= .20 \times .32 = .064$.

The compound probability that the results of roentgen examination are positive and the Pirquet test is negative $= .20 \times .68 = .136$.

The compound probability that the results of roentgen examination are negative and the Pirquet test is positive $= .80 \times .32 = .256$.

If the determination of other probabilities from the data seems desirable, they may be readily computed by dividing the various percentages tabulated in tables 1 and 2 by 100.

The reader is referred to figure 6, which graphically represents the probability that the Pirquet test is negative or positive when various lesions are demonstrable by roentgen examination. This figure shows

rather clearly the high probabilities that the Pirquet test is positive when tuberculous lesions were revealed by films of the chest.

The probabilities presented represent the conditions existing in the group of cases included in this survey. In subsequent similar studies on other groups of children, the finding of probabilities differing from those true for my series of cases will reveal that the different groups investigated are not directly comparable with respect to any of several factors, such as method of study, potency of tuberculin used, type of tuberculin test employed, accuracy of roentgenologic interpretation, incidence of tuberculous infection, etc.

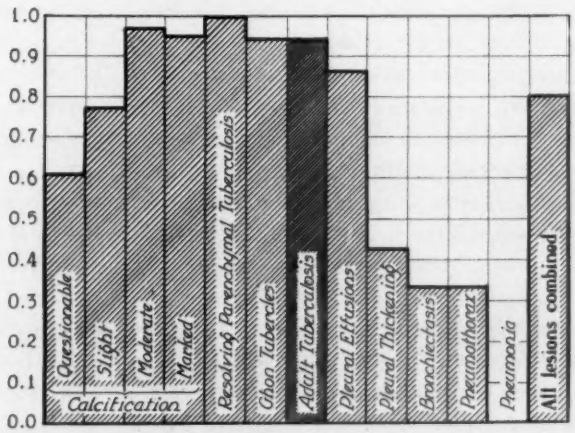

Fig. 6.—The probability that the Pirquet test is negative when various types of lesions are demonstrable by roentgen examinations is indicated by white portions; the probability that the Pirquet test is positive by shaded portions.

COMMENT

It is interesting to theorize and speculate as to the prevailing characteristics of childhood and adult tuberculosis and the relationships existing between these two markedly different conditions. On the basis of speculation, the following points appeal to me as probably outlining the situation:

1. Susceptibility to infection is universal.

2. Resistance to the disease, or the powers with which we are naturally endowed to combat a tuberculous infection, likewise is universal, shows no age variability, but possibly may show an individual variability.

3. This natural resistance which the uninfected infant or adult possesses almost without exception enables one at any age in life to overcome successfully the first infection by the tubercle bacillus, particularly if the infective dosage is small; in the majority of cases one also overcomes relatively heavy infection.

4. Following the first infection the course of the resultant disease in nonfatal cases is practically the same in every instance. The initial lesion tends to recede or resolve, and calcium deposits later appear either in the regional lymph nodes alone or in combination with calcium deposits at the site of the primary focus.

5. Nonfatal tuberculous pulmonary infection occurring the first time uniformly passes through these stages regardless of the age at which it occurs.

6. The adult type of tuberculosis cannot develop from the first infection, and the cases of first infection that resemble the adult type of tuberculosis, in that cavities develop, merely represent overwhelming first infections that the natural powers with which we are endowed to combat tuberculosis are inadequate to conquer.

7. The first infection by the tubercle bacillus alters or replaces the natural power of resistance characteristic of the uninfected person in simultaneously producing an unmeasured beneficial immunity and a detrimental easily demonstrable allergy.

8. Reinfection, either exogenous or autogenous, of a person whose natural resistance has been altered as a result of a primary infection, is prone to result in the development of the crippling and fatal adult type of tuberculosis.

9. The altering of the immunity status of the human body resulting from the first infection by the tubercle bacillus prevents the individual from ever again experiencing the benign form of primary childhood tuberculosis on reinfection. From that date on the soil is prepared for reinfection to result in the development of the adult type of pulmonary tuberculosis with its tendency to cause toxicity, cavitation, hemorrhage and death, due in considerable measure to the deleterious effects of the allergy overbalancing the protective immunity developed simultaneously from the initial contact with the organism.

10. Adult pulmonary tuberculosis cannot develop from the primary infection of a nonallergic person by the tubercle bacillus, and reinfections of the lungs of allergic subjects in adequate dosage can result in only one form of the disease—adult pulmonary tuberculosis.

11. If reinfection occurs at times when the patient is highly allergic, the resultant disease spreads rapidly, whereas if reinfection occurs when allergy is very low, the condition assumes a more chronic course.

12. The first infection by the tubercle bacillus is distinctly detrimental, since thereafter the patient is unable to combat further infection by the tubercle bacillus as successfully as the uninfected person.

13. No attempts should be made to immunize patients artificially unless the immunization can be accomplished without the development of allergy.

14. The production of active immunity without the development of allergy should not be employed until definite proof is established that such immunity is superior to the natural powers possessed by the uninfected infant and adult.

15. To date there is no proof that the unmeasured natural powers for resistance of the uninfected person to combat tuberculosis need be improved on or can be improved.

16. There is ample proof, however, that the need of protection from infection and reinfection is great. In achievement of this end lies the hope in controlling tuberculosis.

The opinions and speculations previously enumerated in general outline the impressions that I have gained as a result of observations and experiences covering the past ten years' work at the Lymanhurst School for Tuberculous Children. On the basis of these observations combined with experiences published by others, some of the points listed may now be considered as established facts. Several of these statements probably must still be considered as unproved speculations, concerning the truth of which, no doubt, many are skeptical. At least, the opinions stated that lack definite proof challenge views to the contrary entertained by many with regard to certain features of primary and secondary tuberculous infections and the relationships existing between these two conditions. For the present, therefore, the advisability of remaining open-minded with regard to many phases of the question and of continuing the search for the truth seems apparent.

SUMMARY

1. This report is based on a study of 5,816 children, including 3,981 (68.4 per cent) and 1,835 (31.6 per cent) children having negative and positive Pirquet tests, respectively.

2. In 1,179 children, or 20.3 per cent of the entire group of 5,816 persons, intrathoracic disease was revealed by roentgen examination.

3. The prevailing type of lesions found in these 1,179 children was that produced by the first infection by the Mycobacterium tuberculosis, as shown by the fact that childhood tuberculosis was found in 82.3 per cent (970 instances) of these cases.

4. For the 3,981 children having a negative Pirquet test, intrathoracic disease was reported in only 6.4 per cent of the cases (255 children), of which 3.9 per cent (154 cases) had lesions characteristic of the childhood type of tuberculosis.

5. If questionable and slight intrathoracic glandular calcifications are excluded, the data show that the more conspicuous lesions characteristic of childhood primary tuberculosis were found in only 0.58 per cent (23 cases) of the children with a negative Pirquet test.

6. For the 1,835 children having a positive Pirquet test intrathoracic disease was discovered by roentgen examination in 50.4 per cent (924 cases), and 44.5 per cent (816 children) had lesions of the childhoood type of tuberculosis.

7. When questionable and slight intrathoracic glandular calcifications are excluded, the more conspicuous and readily identified lesions typical of tuberculosis of first infection were found in 25.9 per cent (475 cases) of the 1,835 children with a positive Pirquet test.

8. If a value of 100 per cent is assigned to the Pirquet test as measuring its efficiency in the discovery of childhood tuberculosis, the roentgen examination has a reliable efficiency of about 25 per cent, and the physical examination an efficiency of a small fraction of 1 per cent.

Childhood Type of Pulmonary Tuberculosis.—1. Resolving parenchymal tuberculous lesions of first infection were found exclusively in the cases with positive tuberculin tests, constituting about 3.6 per cent (66 cases) of this group. With advancing age, the percentage yearly frequency with which resolving parenchymal lesions were found increased to a maximum of 22.2 per cent in the second year of life, but thereafter tended generally toward a progressive annual decline, and were rarely found after the eleventh year.

2. Questionable calcifications of the intrathoracic lymph nodes were reported in 1.5 per cent (59 cases) of the 3,981 children whose Pirquet test was negative and in 5.1 per cent (94 cases) of the 1,835 children whose tuberculin test was positive.

3. Slight calcifications of these glands were reported in 1.8 per cent (72 cases) of the group with negative tuberculin tests and in 13.5 per cent (247 cases) of the group with positive tests.

4. Moderate degrees of calcification of the lymph nodes at the root of the lungs were rarely reported (4 cases only) in the 3,981 children with negative Pirquet tests, which for these cases was an incidence of only 0.1 per cent, as compared with an incidence of 6.05 per cent (111 cases) for those with a positive tuberculin test.

5. Marked calcifications of the hilus glands were found less often relatively than the other degrees of calcification previously mentioned, in both the group in which the tuberculin test was negative and that in which it was positive, being reported in only 0.025 and 1.04 per cent of each group, respectively.

6. Ghon tubercles were discovered in 0.45 per cent (18 children) of the group with a negative Pirquet test, and in 15.2 per cent (279 cases) of those with a positive tuberculin test. The degree of intrathoracic glandular calcification accompanying Ghon tubercles varied from questionable to marked, with the moderate and marked degrees of calcification predominating.

7. From the standpoint of the appearance of lesions discovered by roentgen examination, childhood pulmonary tuberculosis of first infection may be divided into the following three types: (1) resolving pneumonic-appearing parenchymal consolidations, which represent early stages of the disease; (2) intrathoracic glandular calcifications of various degrees, which represent late permanent stages of the disease; (3) Ghon tubercles associated with hilar gland calcifications, which represent late and permanent stages of the disease. These various types of lesions merely represent various developmental stages in the evolution of the disease produced by a primary tuberculous infection, between which many transitional stages may be noted. The end-result in nonfatal cases is always the same in that calcification of the hilus glands appears, or that Ghon tubercles develop associated with calcification of the homolateral hilus glands.

Adult Tuberculosis.—In the group of 3,981 children whose Pirquet test was negative 0.075 per cent (3 cases) were found to have adult pulmonary tuberculosis, whereas in the 1,835 children whose tuberculin test was positive this type of lesion was present in 2.5 per cent (45 instances). In this group of 45 children unmistakable evidence was discovered of the recent development of lesions of the adult type of tuberculosis superimposed on and postdating previously existing quiescent lesions of childhood tuberculosis.

Questionable Tuberculous Lesions.—Pleural thickenings and effusions were found in only a small percentage of the groups with negative and positive Pirquet tests, but tended, however, to occur with greater frequency in infected than in uninfected children.

Nontuberculous Lesions.—There was no increase in the incidence of bronchiectasis, pneumonia or pneumothorax among children with a positive tuberculin test as compared with children with a negative Pirquet test. These conditions were found in only a small percentage of the entire group studied.

Prevailing Type of Lesion.—The prevailing type of lesions demonstrable by roentgen examination of the chest of children is that which results from the primary or first infection by the Mycobacterium tuberculosis.

HUMAN MILK STUDIES

IX. VARIATIONS IN THE COMPOSITION OF MILK AT FOUR HOUR INTERVALS DURING THE DAY AND NIGHT *

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DETROIT

Variations in the percentage composition of human milk are known to occur during the twenty-four hour day, but the desultory procedures followed in sampling the milk leave us without precise knowledge of the extent and nature of these fluctuations and their physiologic and clinical significance. Talbot [1] suggested that the most characteristic picture of the composition of a milk can be ascertained from a sample taken at 9 or 10 in the morning. However, reports of wide fluctuations of milk fat at different nursings suggested that an entire day's production of milk should be collected in order to gain definite information on its characteristic percentage composition.[2]

Roberton [3] aptly remarked that "Woman's milk varies in quality more than any other milk—a fact one might expect *a priori* from the

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* The following approved chemical methods of milk analysis were used in this investigation: the micro-Babcock method for fat; the method for total solids used by the Association of Official Agricultural Chemists; the Kjeldahl method for total nitrogen; the A. O. A. C. method 1 for separation and determination of casein and albumin; the Shaffer-Hartmann method for lactose (except in study X on subject 6 and study VI on subject 8, in which lactose was calculated by difference); the Clark method for calcium; the Fiske and Subbarrow method for phosphorus, and the Van Slyke method for chlorides. For details see Macy, Nims, Brown and Hunscher: Human Milk Study: VII, Am. J. Child. Dis. **42**:569 (Sept.) 1931.

† Deceased.

1. Talbot, F. B.: The Analysis of Human Milk, J. A. M. A. **73**:662 (Aug. 30) 1919.

2. Morse, J. L., and Talbot, F. B.: Diseases of Nutrition and Infant Feeding, New York, The Macmillan Company, 1915, p. 114.

3. Hamill, S. McC.: A Review of Some Older Writings on Maternal Nursing, Am. J. Obst. **47**:333, 1903. Roberton, J.: Observations on the Mortality and Physical Management of Children, London, 1807; cited by Hamill.

endless variety and from the mode of living and circumstances of women." In view of the inconstancy in composition of human milk and the many factors that may have a determinant influence on milk secretion, it is of interest to observe under standardized methods of sampling and analysis the magnitude and trend of variations that occur in its composition at periodic nursing intervals throughout the day and night. The effect of changes in the milk on the nutritional status of the infant and the significance of the daily routine of the mother, including her food, sleep, activities, exercise and emotional condition, merit detailed investigation.

TABLE 1.—*Case Histories*

Description	Lactation	Study	Date of Study	Period in Lactation		Body Weight, Kg.		Comment
				Day	Week	Mother	Baby	
Subject 6.....	A	I	11/22/26	40	6	69.0	4.4	Tripara, 25 years old,
Intelligence, average		II	12/20/26	69	10	68.1	5.2	average daily milk
Education, elementary		III	1/18/27	98	14	67.6	5.7	output 2,600 cc.
Husband's occupation,		IV	2/15/27	126	18	65.4	6.4	
railroad fireman		V	3/15/27	154	22	64.9	6.8	
Type of home,		VI	5/ 2/27	202	27	64.9	7.5	
six room single		(4)	12/ 5/27	419	60	64.0	12.9	
		(5)	12/ 6/27	420	60	64.0	12.9	
		(6)	12/ 7/27	421	60	64.0	12.9	
	B	X	10/22/29	428	61	65.4	12.4	Quartipara, 27 years old, average daily milk output 3,134 cc.
Subject 7.....	A	I	1/ 3/27	44	6	65.8	6.3	Duipara, 33 years old,
Intelligence, superior		II	2/ 1/27	73	10	65.8	7.5	average daily milk
Education, 2 years college		III	3/ 3/27	103	14	65.8	8.6	output 2,000 cc.
Husband's occupation,		IV	3/29/27	129	18	65.8	9.0	
salesman		(4)	10/28/27	342	50	64.0	12.9	
Type of home,		(5)	10/29/27	343	50	64.0	12.9	
six room single		(6)	10/30/27	344	50	64.0	12.9	
Subject 8.....	A	VII	6/ 6/27	244	35	....	....	Primipara, 27 years old
Intelligence, low average								
Education, elementary	B	VI	9/25/29	435	63	81.3	11.3	Duipara, 29 years old,
Husband's occupation, railroad conductor								average daily milk output 1,419 cc.
Type of home, six room single								

Chemical analyses [1] have been made on milk collected under standardized procedures at successive four hour intervals throughout an entire day and night intermittently in the lactation cycle, and in two instances over a consecutive seventy-two hour period. A total of 114 samples of breast milk expressed at four hour intervals throughout nineteen days and nights are included in the analysis. Three women (table 1), who were producing appreciable quantities of milk and were skilled in manually expressing all of their milk, assisted as interested and cooperative subjects of this investigation. Since we have observed a considerable disparity in the composition of the milk secreted during the first and last halves of a nursing period,[4] rigid care was taken to

4. Macy, I. G.; Nims, B.; Brown, M., and Hunscher, H. A.: Human Milk Studies: VII. Chemical Analysis of Milk Representative of the Entire First and Last Half of the Nursing Period, Am. J. Dis. Child. **42**:569 (Sept.) 1931.

obtain all of the milk secreted from both breasts over a definite interval of time for the chemical determinations. These studies are, therefore, in contrast to the many based on samples of milk representative of a given time during a nursing period, of only one breast and of irregular times of the day.

Detailed observations were made in the homes by one of us (H. A. H.) to whose presence the family had been accustomed through her frequent visits and who, therefore, did not disturb the customary family routine or inhibit the characteristic activities of the subjects. During these visits the food was weighed, records were kept of the amount, kind and time of food and fluid intake, and notes were made on the degree and kind of activities of the subjects and their emotional demeanor, important incidents happening during the study, the home atmosphere and other pertinent factors.

The milk collections were begun at 10 a. m., after both breasts had been completely emptied at 6 a. m., and were continued throughout the day at four hour intervals until 6 a. m. the following morning. There were thus six complete samples for analysis during the twenty-four hour period.

EXPERIMENTAL DATA

Daily characteristic trends are shown in the fat content of the milk. Chart 1 represents the variations in fat content (grams per hundred cubic centimeters) of the milk throughout the day and night for subject 6 on intermittent days in the lactation period and is characteristic of the trend for all three subjects. A sharp rise from 6 a. m., to 10 a m., a precipitous drop from 10 a. m. to 2 p. m. and small irregular fluctuations from 6 p. m. to 6 a. m. are demonstrated.

In chart 2 are shown the curves representative of the total solids (grams per hundred cubic centimeters of milk) for studies on subjects 6, 7 and 8. Behaving like fat, the peak of concentration of total solids occurs at 10 a. m., preceded by an abrupt increase from 6 in the morning and followed by a sharp decrease to 2 in the afternoon.

The maximum and minimum values of fat, total solids, nonfat-solids and protein for each day studied, the hours at which they occurred, and the percentages of difference between them are recorded in table 2. The percentage of difference between the high and low values of fat ranged between 14 and 68 and averaged 36. On fifteen of the nineteen days of observation (including all subjects), the maximum value of fat fell at 10 a. m., as shown in the distribution diagram of chart 3. Minimum values occurred at 10 p. m. on four days and at 2 a. m. on nine days, demonstrating the tendency toward a lower concentration of fat at night.

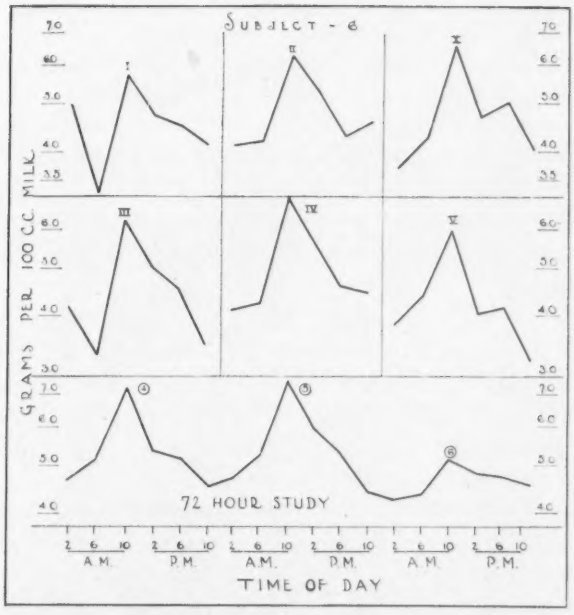

Chart 1.—Curves showing the daily variation of fat in human milk at periodic four hour intervals throughout the day and night. The time in hours is plotted on the horizontal arithmetic scale and grams of fat per hundred cubic centimeters of milk on the vertical logarithmic scale, showing relative rates of change as well as absolute values of milk components during the twenty-four hour day.

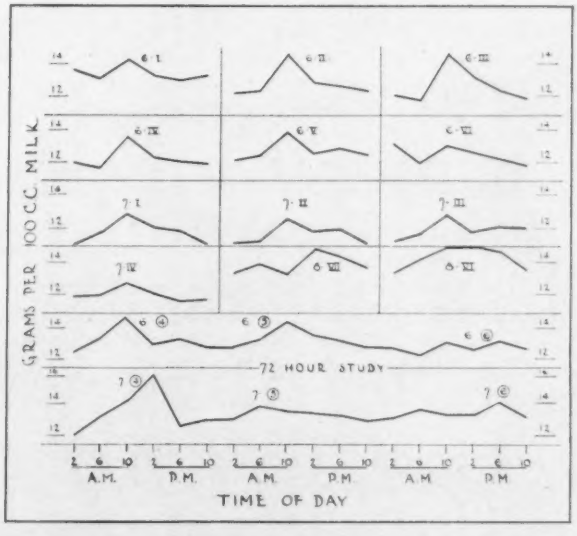

Chart 2.—Curves (plotted semilogarithmically) showing the daily variation of total solids in breast milk at periodic four hour intervals throughout the day and night.

TABLE 2.—*Daily Maximum and Minimum Values of Milk Constituents and Their Hour of Occurrence* *

Subject	Study	Fat					Protein					Lactose					Total Solids				
		Maximum	Time	Minimum	Time	Percentage of Difference	Maximum	Time	Minimum	Time	Percentage of Difference	Maximum	Time	Minimum	Time	Percentage of Difference	Maximum	Time	Minimum	Time	Percentage of Difference
6	I	5.69	10 a.m.	3.30	6 a.m.	42	1.214	6 p.m.	1.168	10 a.m.	4	8.33	6 a.m.	6.88	6 p.m.	17	14.28	10 a.m.	12.88	6 p.m.	10
	II	6.36	10 a.m.	4.13	2 a.m.	35	1.124	2 p.m.	1.071	10 a.m.	5	7.44	6 p.m.	7.33	6 a.m.	2	14.52	10 a.m.	12.17	2 a.m.	16
	III	6.24	10 a.m.	3.35	6 a.m.	46	1.081	2 p.m.	1.013	10 p.m.	6	7.22	10 p.m.	6.88	6 a.m.	5	14.49	10 a.m.	11.65	6 a.m.	20
	IV	5.98	10 a.m.	3.25	10 p.m.	46	1.102	2 p.m.	1.066	10 p.m.	3	7.45	10 p.m.	7.17	10 a.m.	4	13.48	10 a.m.	11.66	6 a.m.	14
	V	7.08	10 a.m.	4.15	2 a.m.	41	1.137	6 p.m.	1.043	10 p.m.	8	7.31	2 p.m.	7.10	6 p.m.	3	13.69	10 a.m.	12.06	2 a.m.	12
	VI	5.35	2 a.m.	3.55	2 p.m.	34	1.060	2 p.m.	0.899	2 a.m.	10	7.67	2 p.m.	6.64	12 a.m.	13	13.08	2 a.m.	11.84	10 p.m.	9
	(4)	7.15	10 a.m.	4.47	10 p.m.	37	1.180	2 p.m.	1.034	2 a.m.	12	6.88	10 p.m.	6.02	10 a.m.	13	14.45	10 a.m.	12.37	2 a.m.	14
	(5)	7.38	10 a.m.	4.38	10 p.m.	41	1.203	2 p.m.	1.053	6 p.m.	12	6.90	10 p.m.	6.24	2 p.m.	10	14.14	10 a.m.	12.57	2 a.m.	11
	(6)	5.06	10 a.m.	4.22	2 a.m.	17	1.299	2 p.m.	1.050	10 p.m.	19	7.02	2 a.m.	6.15	2 p.m.	12	12.89	6 p.m.	12.10	6 a.m.	6
	X	6.62	10 a.m.	3.76	2 a.m.	43	1.000	6 p.m.	0.924	10 p.m.	8	7.23	2 a.m.	5.09	10 a.m.	30	12.87	10 a.m.	11.57	2 p.m.	10
7	I	5.91	10 a.m.	2.06	2 a.m.	65	1.026	6 p.m.	0.930	10 p.m.	9	7.76	6 p.m.	6.10	10 a.m.	21	12.80	10 a.m.	11.05	10 p.m.	14
	II	4.78	10 a.m.	2.63	2 a.m.	45	0.996	2 a.m.	0.962	10 p.m.	3	7.31	10 p.m.	7.05	2 a.m.	4	12.41	10 a.m.	11.21	10 p.m.	10
	III	4.99	6 p.m.	1.60	6 a.m.	68	1.057	6 p.m.	0.953	6 a.m.	10	7.29	2 a.m.	7.12	10 a.m.	2	12.76	10 a.m.	11.22	2 a.m.	12
	IV	4.94	2 a.m.	3.87	6 p.m.	22	1.006	2 a.m.	0.910	10 a.m.	10	6.86	2 a.m.	6.60	6 a.m.	4	12.64	10 a.m.	11.61	6 p.m.	8
	(4)	6.12	10 a.m.	4.84	6 p.m.	21	1.177	10 a.m.	1.094	6 a.m.	7	3.21	2 p.m.	5.69	10 p.m.	38	15.86	2 p.m.	11.93	2 a.m.	25
	(5)	7.07	10 a.m.	5.31	10 p.m.	25	1.173	6 p.m.	1.075	10 p.m.	8	6.46	6 a.m.	5.57	2 a.m.	14	13.57	6 a.m.	12.72	10 p.m.	6
	(6)	6.06	6 p.m.	5.20	2 a.m.	14	1.257	2 p.m.	1.164	10 p.m.	7	6.37	6 a.m.	5.60	10 p.m.	12	13.78	6 p.m.	12.91	2 a.m.	6
8	VII	5.92	2 p.m.	4.59	10 a.m.	22	1.228	6 p.m.	1.094	6 a.m.	11	6.78	6 a.m.	6.70	6 p.m.	1	14.58	2 p.m.	13.10	10 a.m.	10
	VI	7.04	12 p.m.	5.07	2 a.m.	28	1.223	2 p.m.	1.140	2 a.m.	7	7.03	6 a.m.	6.53	10 a.m.	7	15.05	2 p.m.	13.09	2 a.m.	13
Percentage of difference: Range				14 to 68					3 to 19					2 to 38					4 to 25		
Average				36					8					11					12		

* In grams per hundred cubic centimeters.

On twelve of the nineteen days, the highest concentration of total solids fell at 10 a. m. As in the case of fat, there is a tendency toward a higher concentration of solids during the day and a lower concentration during the night, as demonstrated by the greater frequency of minimum values at 10 p. m. and 2 a. m. The percentage of difference between high and low values ranged between 4 and 25 and averaged 12.

The phenomena of variation in the percentage composition of milk at different times of the day have attracted the interest of numerous observers, who have especially noted the higher concentrations of fat and solids during the day.[5] The characteristic picture presented by the daily fat fluctuations is similar to that reported by St. Engel [6] and practically identical with that more recently demonstrated by Deem.[7]

It is of interest to call attention to similar findings from dairy science experiments. The milk of cows and goats has been observed to vary during different times of the day, the volume of milk varying most, the fat content somewhat less, and protein, sugar and ash content very little.[8] Cow's milk shows a high fat content at midday [9] and a low fat content in the early morning.[10] It has been concluded that there is some factor operating during the night to lower the fat content of the early morning milk, independently of a long or short milking interval.[11] There is a tendency for the volume of milk to decrease

5. Pfeiffer, E.: Beiträge zur Physiologie der Muttermilch und ihren Beziehungen zur Kinderernährung, Jahrb. f. Kinderh. **20**:359, 1883. Johannessen, A., and Wang, E.: Studien über die Ernährungsphysiologie des Säuglings, Ztschr. f. physiol. Chem. **24**:482, 1898. Adriance, V., and Adriance, J. S.: A Clinical Report on the Chemical Examination of Two Hundred Cases of Human Breast Milk, Arch. Pediat. **14**:22, 1897. St. Engel: Ueber einige Fragen der Frauenmilchsecretion insbesondere über die Secretion des Milchfettes, Arch. f. Kinderh. **53**:241, 1910. Helbich, H.: Die Variationem der Milchmenge und ihre Beziehungen zum Fettgehalt, Monatschr. f. Kinderh. **10**:649, 1911. Denis, W., and Talbot, F. B.: A Study of the Lactose, Fat and Protein Content of Women's Milk, Am. J. Dis. Child. **18**:93 (Aug.) 1919. Deem, H. E.: Observations on the Milk of New Zealand Women, Arch. Dis. Childhood **6**:53, 1931.

6. St. Engel (footnote 5).

7. Deem (footnote 5).

8. Dyssegaard, A.: Investigations of Milk Secretion, Experiment Station Record, 1924, no. 50, p. 277; Chem. Abstr. **18**:2367, 1924.

9. Eckles, C. H., and Shaw, R. H.: Variations in the Composition and Properties of Milk from the Individual Cow, Bull. 157, Bur. Animal Indust., U. S. Dept. Agric., 1913, p. 27

10. Bartlett, S.: Studies in Milk Secretion Based on the Variations and Yields of Milk and Butter Fat Produced at Morning and Evening Milkings, J. Agric. Sc. **19**:36, 1929.

11. Campbell, K. W. D.: Milking at Three Eight-Hour Intervals as a Means of Investigating Variations in the Fat and Solids-Not-Fat, J. Agric. Sc. **20**:213. 1930.

during the day and increase during the night (chart 3). A range of from 10 to 41 with an average of 25 per cent of difference was found in the largest and smallest amounts of milk secreted at four hour intervals during a single day. This is in accord with the observations of St. Engel [6] and Denis and Talbot,[12] who have noted a progressive diminution in the amount of milk secreted as the day advances, reaching a minimum in the afternoon.

The volume of milk secreted during the day bears an interesting relation to the distribution of high and low concentrations of lactose and water. Lactose has frequently been designated the most constant of all milk constituents [13] and is further described as the regulator of milk

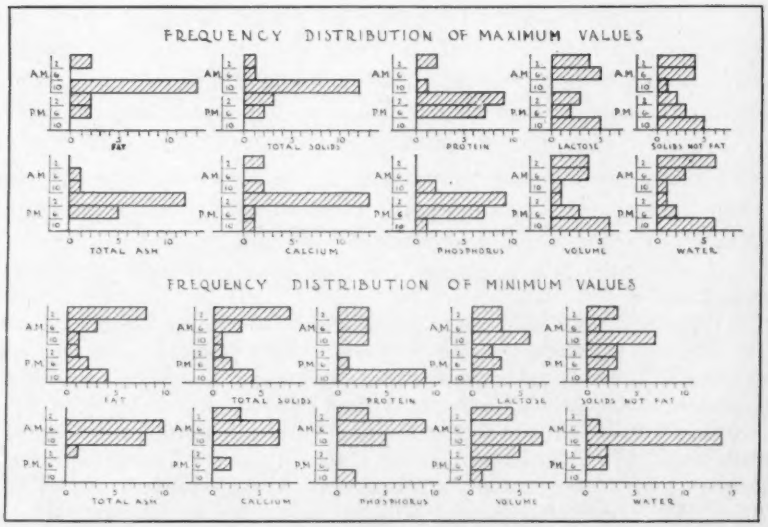

Chart 3.—Graphs showing the frequency distribution of maximum and minimum values of human milk components at periodic four hour intervals. The observation periods totaled nineteen days. The horizontal scale shows the number of days on which the values noted were obtained.

volume.[14] A tendency toward higher concentrations of both water and lactose with greater volume of milk at night and lower concentrations with decreased volume of milk during the day is indicated. Moreover, the coincidence of the distribution of the maximum values of fat and

12. Denis and Talbot (footnote 5).

13. Talbot, F. B.: A Summary of Present Knowledge of Human Milk, Am. J. Dis. Child. **7**:445 (June) 1914.

14. Taylor, W., and Husband, A. D.: The Effect on the Percentage Composition of the Milk of (*a*) Variations in the Daily Volume and (*b*) Variations in the Nature of the Diet, J. Agric. Sc. **12**:111, 1922.

the minimum values of water, as shown by chart 3, suggests an inverse relationship between the two.

The percentage of difference between maximum and minimum values of total nitrogen ranged between 3 and 19 with an average of 8. There is a rise in concentration in the afternoon, as shown by the distribution of maximum values at 2 and 6 p. m. Thus under the conditions of these experiments, the total nitrogen shows a characteristic daily behavior—a result contrary to the findings recorded in the literature.[7]

The curves representative of the total ash, calcium and phosphorus of the milk at each four hour interval throughout the twenty-four hour

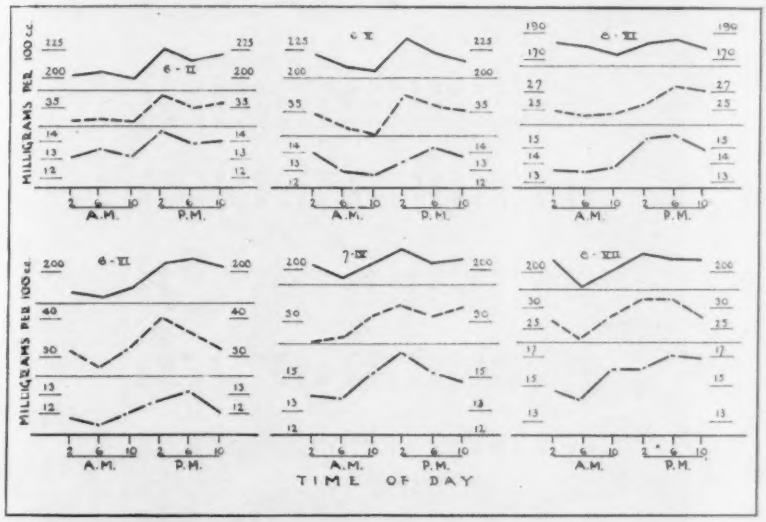

Chart 4.—Curves (plotted semilogarithmically) showing the daily variation of total ash, calcium and phosphorus of breast milk at periodic four hour intervals throughout the day and night. In this and in chart 5 the solid line indicates ash; the even broken line, calcium, and the uneven broken line, phosphorus.

day demonstrate regular and definite changes (charts 4 and 5). The total ash content shows a sharp increase from a minimum at 6 and 10 a. m. to a maximum at 2 p. m. The calcium and phosphorus contents vary similarly, the preponderance of minimum values occurring at 6 or 10 a. m. and the maximum at 2 p. m. Percentages of difference ranged as follows: total ash, 5 to 29; calcium, 4 to 29, and phosphorus, 7 to 34. The average percentages of difference of total ash, calcium and phosphorus were 11, 14 and 15, respectively. The curves showing the total ash, calcium and phosphorus are plotted semilogarithmically, so that relative rates of change among the three constituents as well as

TABLE 3.—*Daily Maximum and Minimum Values of Milk Volume, Water and Solids-Not-Fat, and Their Hour of Occurrence*

Subject	Study	Volume, Cc.					Water, Cc.					Solids-Not-Fat, Gm.				
		Maximum	Time	Minimum	Time	Percentage of Difference	Maximum	Time	Minimum	Time	Percentage of Difference	Maximum	Time	Minimum	Time	Percentage of Difference
6.....	I	590	10 p.m.	428	2 a.m.	27	90.71	6 p.m.	89.08	10 a.m.	2	9.75	6 a.m.	8.32	6 p.m.	15
	II	542	6 a.m.	428	2 p.m.	21	91.10	2 a.m.	88.59	10 a.m.	3	8.20	6 p.m.	7.46	2 p.m.	9
	III	590	2 a.m.	532	6 p.m.	10	91.30	6 a.m.	88.35	10 a.m.	3	8.37	10 p.m.	7.66	6 p.m.	8
	IV	615	6 p.m.	410	10 a.m.	33	91.42	6 a.m.	89.60	10 a.m.	2	8.57	10 p.m.	7.18	6 a.m.	16
	V	574	6 p.m.	477	2 p.m.	17	90.94	2 a.m.	89.31	10 a.m.	2	8.12	6 p.m.	6.61	10 a.m.	19
	VI	600	6 p.m.	370	2 p.m.	38	91.19	10 p.m.	90.06	10 a.m.	1	8.94	2 p.m.	7.73	2 a.m.	14
	(4)	338	2 a.m.	252	2 p.m.	25	90.50	2 a.m.	88.30	10 a.m.	2	8.12	10 p.m.	7.30	10 a.m.	10
	(5)	370	2 a.m.	286	10 a.m.	23	90.46	10 p.m.	88.74	10 a.m.	2	8.23	10 p.m.	6.76	10 a.m.	18
	(6)	356	2 a.m.	275	10 a.m.	23	90.98	6 a.m.	90.08	6 p.m.	1	8.32	2 a.m.	7.66	2 p.m.	8
	X	508	10 p.m.	442	6 p.m.	13	91.80	2 p.m.	90.59	10 a.m.	1	8.36	2 a.m.	6.25	10 a.m.	25
7.....	I	474	10 p.m.	418	2 a.m.	12	92.23	10 p.m.	90.30	10 a.m.	2	9.03	2 a.m.	6.89	10 a.m.	24
	II	531	6 a.m.	343	10 a.m.	35	92.12	10 p.m.	90.92	10 a.m.	1	8.60	2 a.m.	7.29	2 p.m.	15
	III	607	2 p.m.	359	10 a.m.	41	91.64	2 a.m.	90.18	10 a.m.	2	9.98	6 a.m.	6.09	6 p.m.	39
	IV	432	10 p.m.	365	2 a.m.	16	91.54	6 p.m.	90.36	10 a.m.	1	8.06	10 a.m.	6.93	2 a.m.	14
	(4)	278	6 a.m.	110	2 a.m.	60	91.16	2 a.m.	87.22	2 p.m.	4	10.61	2 p.m.	6.97	10 p.m.	34
	(5)	225	6 a.m.	174	10 a.m.	23	90.29	10 p.m.	89.42	6 a.m.	1	7.74	6 a.m.	6.24	10 a.m.	19
	(6)	242	10 p.m.	170	10 a.m.	30	90.15	10 p.m.	89.31	6 p.m.	1	7.72	6 p.m.	6.94	10 p.m.	10
8.....	VII	116	10 a.m.	88	10 p.m.	24	89.95	10 a.m.	88.38	2 p.m.	1	8.83	10 p.m.	8.04	2 a.m.	9
	VI	249	10 p.m.	202	2 p.m.	30	90.37	2 a.m.	88.38	10 a.m.	1	8.40	6 a.m.	7.86	10 a.m.	6
Range of percentage of difference.....				10 to 41					1 to 4					6 to 39		
Average percentage of difference.....				26					2					16		

absolute values are shown. The corresponding curves for each day appear similar and in some instances almost identical. It is thus suggested that the total ash, calcium and phosphorus have the same rate of change thorughout the day, indicating that they are intimately associated in the physiologic mechanism of milk secretion.

Little attention has been given to the mineral constituents and their fluctuations at the successive nursing periods, since the general opinion has been that the ash components remain constant. The work of Barbier and Mascré [15] included determinations of total ash at 4 a. m.,

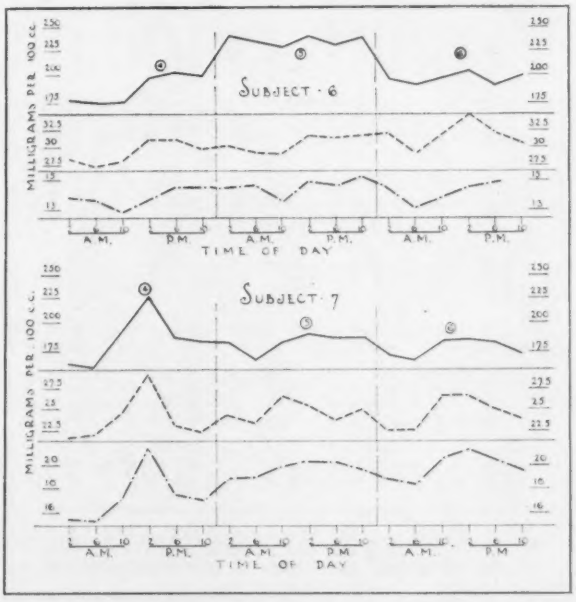

Chart 5.—Curves (plotted semilogarithmically) showing the daily variation of total ash, calcium and phosphorus of breast milk at periodic four hour intervals over a seventy-two hour period.

11 a. m. and 5 p. m., which showed the 11 a. m. sample to be more concentrated in total ash. Hunaeus,[16] however, observed no regular difference in the calcium oxide content of the morning and evening milk. Determination of various physical constants of human milk,

15. Barbier, H., and Mascré: Note sur les variations des sels minéraux du lait de femme aux différentes heures de la journée, Bull. Soc. de pédiat. de Paris **13**: 260, 1911.

16. Hunaeus: Ueber den Kalkgehalt der Frauenmilch, Biochem. Ztschr. **22**:442, 1909.

TABLE 4.—*Daily Maximum and Minimum Values of Milk Constituents and Their Hour of Occurrence* *

Subject	Study	Total Ash					Calcium					Phosphorus					Chlorine				
		Maximum	Time	Minimum	Time	Percentage of Difference	Maximum	Time	Minimum	Time	Percentage of Difference	Maximum	Time	Minimum	Time	Percentage of Difference	Maximum	Time	Minimum	Time	Percentage of Difference
6	I	234	6 p.m.	202	10 a.m.	14	39.7	2 p.m.	28.1	10 a.m.	29	15.7	6 p.m.	12.6	10 a.m.	20					
	II	228	2 p.m.	200	10 a.m.	12	36.9	2 p.m.	33.1	10 a.m.	10	14.7	2 p.m.	13.1	2 a.m.	20					
	III	238	2 p.m.	206	10 a.m.	13	37.6	2 a.m.	34.5	10 a.m.	11	14.6	2 p.m.	13.1	6 a.m.	10	38.2	6 a.m.	25.9	6 p.m.	32
	IV	223	2 p.m.	207	10 a.m.	7	35.7	10 p.m.	28.6	10 a.m.	20	13.6	2 p.m.	12.2	10 a.m.	10					
	V	238	2 p.m.	210	10 a.m.	12	37.7	2 p.m.	31.9	10 a.m.	15	14.3	6 p.m.	12.8	10 a.m.	10	38.0	10 a.m.	32.2	10 p.m.	15
	VI	210	6 p.m.	179	6 a.m.	15	35.0	2 p.m.	28.6	6 a.m.	18	13.2	6 p.m.	11.4	6 a.m.	14					
	(4)	196	6 p.m.	175	6 a.m.	11	31.0	2 p.m.	27.3	6 a.m.	12	14.4	6 p.m.	12.8	10 a.m.	14					
	(5)	188	2 p.m.	176	10 a.m.	6	31.7	2 p.m.	29.0	10 a.m.	9	14.7	2 p.m.	13.5	10 a.m.	8					
	(6)	213	2 p.m.	189	6 a.m.	11	34.8	2 p.m.	28.9	6 a.m.	17	14.8	10 p.m.	13.1	6 a.m.	8					
	X	202	6 p.m.	174	6 a.m.	14	34.9	2 a.m.	29.0	10 a.m.	17	15.4	10 a.m.	12.3	10 p.m.	20					
7	I	218	6 a.m.	207	2 p.m.	5	30.0	2 p.m.	28.8	6 p.m.	4	14.9	6 p.m.	13.8	10 p.m.	7					
	II	207	10 a.m.	195	6 a.m.	6	32.0	10 a.m.	29.0	6 p.m.	9	20.5	10 a.m.	13.5	6 a.m.	34					
	III	214	2 p.m.	202	10 a.m.	6	34.9	2 p.m.	30.4	6 a.m.	13	15.6	2 p.m.	14.0	2 a.m.	10	45.9	6 a.m.	40.3	2 p.m.	12
	IV	221	2 p.m.	196	6 a.m.	11	32.0	2 p.m.	27.7	2 a.m.	13	16.7	2 p.m.	13.7	6 a.m.	18	42.1	6 a.m.	35.4	10 a.m.	16
	(4)	227	2 p.m.	161	6 a.m.	29	29.3	2 p.m.	21.7	2 a.m.	26	21.5	2 p.m.	15.3	6 a.m.	29					
	(5)	187	2 p.m.	167	6 a.m.	11	26.2	10 a.m.	23.1	6 a.m.	12	17.7	2 p.m.	16.1	2 a.m.	9					
	(6)	183	2 p.m.	166	6 a.m.	9	26.3	2 p.m.	22.3	2 a.m.	15	18.7	2 p.m.	15.6	6 a.m.	17					
8	VII	218	2 p.m.	188	6 a.m.	14	31.5	2 p.m.	26.5	6 a.m.	16	17.2	6 p.m.	14.2	6 a.m.	17	32.2	2 a.m.	22.1	10 a.m.	31
	VI	187	6 p.m.	175	10 a.m.	6	27.8	6 p.m.	24.5	6 a.m.	8	15.9	6 p.m.	13.6	6 a.m.	14					
Percentage of difference																					
Range				5 to 29					4 to 29					7 to 34					12 to 32		
Average				11					14					14					21		

* In milligrams per hundred cubic centimeters.

such as the depression of the freezing point, electrical conductivity [17] and the cation content,[18] has demonstrated variations during a single day.

In the present studies five complete day analyses of the chloride content of the milk were recorded. The percentage of difference between the maximum and minimum values of the chloride ranged between 12 and 32 with an average of 21. The highest values of chloride are shown in the early morning and late evening samples, and the lowest values during the day (chart 6), an observation that corroborates the findings of Sisson and Denis.[19] Thus the chloride appears to behave unlike the other mineral constituents, with characteristic curves the reverse of those shown by the calcium and phosphorus.

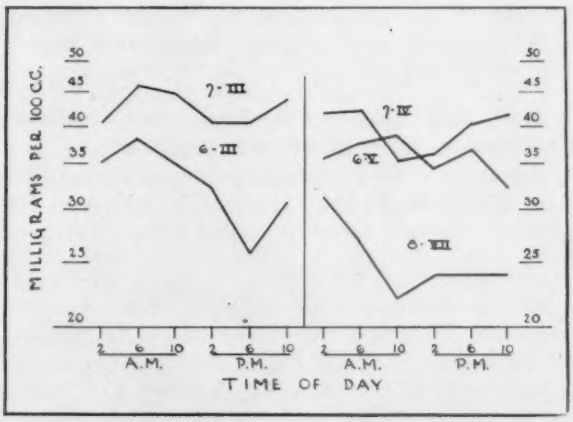

Chart 6.—Curves (plotted semilogarithmically) showing the daily variation in the chloride content of breast milk at four-hour intervals throughout the day and night.

In view of these changes in breast milk and characteristic daily trends in the variation of the fat, total nitrogen, total ash, calcium, phosphorus and chloride components, it is of physiologic significance to ascertain if there are determinant influences that have their origin in the daily routine of the mother.

It is the general opinion that drastic and long continued changes must be made in the food of the mother before the milk composition

17. Koeppe, H.: Vergleichende Untersuchungen über den Salzgehalt der Frauen- und Kuhmilch, Jahrb. f. Kinderh. **47**:389, 1898.

18. Olewsky, M. J.: Der Kationengehalt der Frauenmilch und seine Abhängigkeit vom vegetativen Nervensystem, Jahrb. f. Kinderh. **124**:280, 1929.

19. Sisson, W. R., and Denis, W.: Studies on the Inorganic Constituents of Milk: I. Chlorides in Human Milk, Am. J. Dis. Child. **21**:389 (April) 1921.

is materially affected.[20] From numerous observations it would appear that when the food of the mother is insufficient or excessive in caloric value for an extended period of time, the quality of the milk is altered.[21] A detailed study has been made of the relation between the food intake and habits of the mother and the composition of the milk secreted at four hour intervals throughout the day and night. The data demonstrate that milk constituents act independently, following a characteristic trend during the day and night regardless of the day's dietary. It

20. Lami: Expériences sur la production du lait, Compt. rend Acad. d. sc. **89:** 259, 1879; cited by Overman and Wright. Eckles, C. H., and Palmer, L. S.: The Influence of the Plane of Nutrition of the Cow upon the Composition and Properties of Milk and Butter Fat: The Influence of Underfeeding, Bull. 25, Missouri Agricultural Experiment Station, 1916, p. 107; cited by Overman and Wright. Porcher, C.: L'Inanition et la composition chimique du lait, Compt. rend. Acad. d. sc. **170:** 1461, 1920. Ragsdale, A. C., and Swett, W. W.: Factors Affecting the Composition of Milk, Bull. 179, Missouri Agricultural Experimental Station, 1921, p. 22. Overman, O. R., and Wright, K. E.: The Effect of Inanition upon the Yield and Composition of Cow's Milk, J. Agric. Research **35:**637, 1927. Hart, E. B., and Humphrey, G. C.: Further Studies of the Relation of the Quality of Proteins to Milk Production, J. Biol. Chem. **26:**457, 1916. Hoobler, B. R.: The Effect on Human Milk Production of Diets Containing Various Forms and Quantities of Protein, Am. J. Dis. Child. **14:**105 (Aug.) 1917. Röhmann, F.: Ueber den Einfluss der Ernährung auf die Sekretion der Milchdrüse, Monatschr. f. Geburtsh. u. Gynäk. **47:**455, 1918. Pestalozza, C.: Sue valore energetico del latte di donna, Pediatria **29:**1027, 1921; The Potential Energy in Breast Milk, abstr., J. A. M. A. **78:**251 (Jan. 21) 1922. Pasch, C.: Einwirkung der Unternährung auf den Fettgehalt der Frauenmilch, Zentralbl. f. Gynäk. **45:**744, 1921. Sedgwick, J. P., and Cole, W. C. C.: Breast Feeding and Nutrition, in Abt: Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 591. Maynard, L. A., and McCay, C. M.: The Influence of a Low-Fat Diet upon Fat Metabolism During Lactation, J. Nutrition **2:**67, 1929. Thiemich, M.: Ueber Veränderungen der Frauenmilch durch physiologische und pathologische Zustände, Monatschr. f. Geburtsh. u. Gynäk. **8:**521; 645, 1898. Kerley, C. G.: The Practice of Pediatrics, Philadelphia, W. B. Saunders Company, 1914, p. 24. Banu and Heresco: Recherches sur la sécrétion lactée chez la femme, Compt. rend. Soc. de biol. **92:**531, 1925; abstr., J. A. M. A. **84:**1389 (May 2) 1925. Bahrdt, H., and Edelstein, F.: Des Kalkangebot in der Frauenmilch, Jahrb. f. Kinderh. **72:**16, 1910. Schabad, J. A.: Der Kalkgehalt der Frauenmilch. Zur Frage der ungenügenden Kalkzuführ als Ursache der Rachitis, Jahrb. f. Kinderh. **74:**511, 1911. Zuckmayer, F.: Ueber die Frauenmilch der ersten Laktationszeit und den Einfluss einer Kalk-und Phosphorsäurezulage auf ihre Zusammensetzung, Arch. f. d. ges. Physiol. **158:**209, 1914. Sisson, W. R., and Denis, W.: Observations on the Salt Content of Human Milk, J. A. M. A. **75:**601 (Aug. 28) 1920.

21. Lederer, R.: Ueber Hypogalaktie. I. Qualitative Hypogalaktie. Die Wirkung der Kriegsernährung auf die Zusammensetzung der Frauenmilch, Ztschr. f. Kinderh. **31:**141, 1921. Klotz: Kriegsernährung und Frauenmilch, ibid. **26:**150, 1920. Momm: Die durch die Hungerblockade herabgesetzte Stillfähigkeit der deutschen Frau, München. med. Wchnschr. **67:**783, 1920. Kaupe, W.: Muttermilch und Krieg, Monatschr. f. Kinderh. **15:**83, 1918.

appears, therefore, that some factor other than food plays a rôle in effecting these distinctive changes.

It has been suggested frequently that environment may contribute in an undefined manner to the variations in the composition of human milk.[22] Excessive exercise has been reported to reduce milk flow and moderate exercise to influence favorably the amount and kind of milk produced.[23] Clinicians have recommended adjusting the amount of exercise taken by the mother as a means of modifying certain abnormalities of milk composition.[24] Occasional experiments on cows have been conducted with a view of observing this factor. Cow's milk shows higher fat,[25] specific gravity and refractive index [26] when the cow is given increased exercise.

Rest has been shown to have a salutary influence on the quantity and quality of human milk. Nebert and Koch,[27] who became interested in the stimulating effect of music on human milk production, observed that there was an increased milk flow throughout the entire experimental period, including days with and without music. When the women returned to their homes, the milk supply again diminished, leading the authors to attribute the increased output to the pleasant and restful environment provided during the experimental period, rather than to the music alone. These indications of increased fat content with exercise and increased volume with rest are significant in connection with the distinctive trends found in the variations in the volume and chemical composition of the milk. Thus greater volume was observed at night during the hours of rest, and higher fat in the forenoon after the strenuous activities of the day had been resumed. However, on the days of the studies during which the subjects washed for several hours the typical curves of fat and other constituents remained unaltered —a finding that indicates that factors other than work and rest may subtly operate to change the composition of the milk.

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22. Chapin, H. D., and Royster, L. T.: Diseases of Children, ed. 6, New York, William Wood & Company, 1928, p. 113. Grulee, C. G.: Infant Feeding, ed. 3, Philadelphia, W. B. Saunders Company, 1917, p. 94. Dennett, R. H.: Simplified Infant Feeding, ed. 2, Philadelphia, J. B. Lippincott Company, 1920, p. 229. Changes in Mother's Milk under War Conditions, editorial, J. A. M. A. **73**:1531 (Nov. 15) 1919. Talbot (footnote 13).

23. Rotch, T. M.: Pediatrics, Philadelphia, J. B. Lippincott Company, 1896, p. 191.

24. Morse, J. L.: Clinical Pediatrics, Philadelphia, W. B. Saunders Company, 1926, p. 135. Chapin and Royster (footnote 22).

25. Woodward, T. E.: Factors Influencing Percentage of Fat in Milk, J. Dairy Sc. **6**:466, 1923.

26. Haun, F.: Ztschr. f. Untersuch. Lebensmitt. **54**:337, 1927; Influence of the Work of Cows on the Composition of the Milk, Chem. Abstr. **22**:2599, 1928.

27. Nebert and Koch, E. W.: Zur Frage der Einwirkung der Musik auf die Ergiebigkeit der weiblichen Brust, Monatschr. f. Kinderh. **33**:385, 1926.

Though the lives of these women were quite regular as to the daily routine of meals, sleep, household tasks, etc., many problems concerning the family, children and household activities may arise during the day and influence the quality of the milk through the accompanying emotional disturbances. Clinical observers have recorded variations and changes in the milk concomitant with nervous disturbances, and mention is frequently made of increased protein and fluctuating fat content during such times.[28] A case reported from these laboratories [29] demonstrated that a woman who usually produced milk of satisfactory quality suddenly lost this ability when sickness and financial reverses occurred in the home. The quantity produced was not appreciably affected, but the milk secreted during the emotional strain was very inferior in fat, total protein, solids and ash as well as in calcium and phosphorus. It was not known whether the changes were due to the emotional factor alone or were to be attributed in part to the changed dietetic and hygienic conditions with an accompanying lowering of physiologic efficiency. The case does demonstrate, however, that emotional factors may influence the physiology of milk secretion. In spite of the variety and diversity of emotional conditions experienced by the woman of this investigation on the different days of observation, the various milk components continued to follow their usual characteristic rhythm.

It has been suggested that greater variability is to be expected in the milk of a nervous woman than in that of an even-tempered, emotionally stable mother. In this connection Sisson and Denis [19] conducted unique studies on the chloride content of the milk of numerous women classified as to emotional type. More than 300 per cent of difference was found in the chloride content of samples of milk secreted by an individual woman during the twenty-four hours. However, the chloride in the milk of normal, even-tempered, phlegmatic subjects showed the relatively narrow range of variation of from 30 to 50 mg.

Detailed studies have been made of the emotional make-up of subjects 6, 7 and 8 over a period of three years, and a preliminary report of the findings has been published.[30] Subjects 6 and 8, although sisters,

28. Frost, C. A.: Nerves and the Nursing Mother, Am. J. Obst. **67**:1261, 1913. Griffith, J. P. C., and Mitchell, A. G.: The Diseases of Infants and Children, ed. 2, Philadelphia, W. B. Saunders Company, 1927, vol. 1, p. 104. Chapin and Royster (footnote 22).

29. Macy, I. G., and Outhouse, J.: Breast Milk; A Variable Food, J. Am. Dietet. A. **4**:9, 1928.

30. Hunscher, H. A.; Vincent, E. L., and Macy, I. G.: The Technique of Securing Quantitative and Coordinated Psychological and Physiological Data on Lactating Women in Their Usual Home Environment, Child Development **1**:15, 1930.

were quite different in emotional nature. Subject 6 was of a nervous, high-strung temperament, and her home environment one of agitation and confusion; subject 8 was of a phlegmatic temperament and lived a more serene and satisfying life. A comparison of the variabliity of the various constituents of the milk of subjects 6 and 8 shows a greater variability in the fat content of the milk of subject 6 than in that of subject 8, but the other constituents of the milk of the two subjects exhibited about the same degree of fluctuation (table 5).

Other observers have found regular changes in the milk fat of different women and also in that of goats and cows. Under the conditions of these experiments, with standardized methods of expressing the breast milk at rhythmic four intervals, we found definite daily trends characteristic not only of the fat but also of the other milk components.

TABLE 5.—*Average Coefficient of Variation of Each Milk Constituent Based on Periodic Four Hour Samples Throughout the Day and Night* *

Subject	Fat	Lactose	Total Solids	Total Nitrogen	Total Ash	Calcium	Phosphorus	Calories
6.....	17.0	3.9	4.5	4.1	4.3	5.8	4.8	9.2
7.....	16.5	5.6	4.2	2.9	3.3	5.2	7.8	8.5
8.....	10.6	2.5	4.5	3.4	3.3	5.5	4.9	6.6
Average.....	16.1	4.4	4.4	3.6	3.8	5.5	5.9	8.6

* The coefficients of variation were computed as follows: The deviation of each four hour determination from its corresponding mean of the twenty-four hour day was computed and the standard deviation obtained by the formula

$$S\ D = \sqrt{\frac{\text{sum (deviation from mean)}^2}{6}}$$

The coefficient of variation was then computed by the formula

$$C\ V = \frac{\text{standard deviation}}{\text{mean}} \times 100$$

Since the environment of these women differs so widely, this regularity of trend intimates some peculiarity of mammary gland physiology which, in spite of the day's routine or events, causes a rhythmic fluctuation of the individual milk constituents. The daily variation of other body fluids may also suggest a possible relationship between changes in the blood, the milk and the urine. It is the consensus that the blood constituents remain unusually constant during the day and night and under varying conditions.[31] Combined studies on the fat in the blood and milk of cows gave no evidence of correlation between the fluctuations of the milk fat and those of the blood lipids.[32]

Variations have been observed in the rhythm of excretion of urinary constituents. The daily excretion of phosphates has been shown to vary

31. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, vol. 1, Interpretations, Baltimore, Williams & Wilkins Company, 1931.

32. Porcher, C., and Maynard, L.: Lait **10**:601 and 765, 1930; The Fat of the Blood and the Fat of the Milk During Lactation, Chem. Abstr. **25**:328, 1931.

even during complete rest and starvation.[33] An increased excretion of phosphates has been reported coincident with sleep at night,[34] but others have observed a minimal rate of excretion in the early hours of the day and a maximal rate in the afternoon—a trend which simulates that observed in the milk.[35]

Although of preliminary nature, the results here reported not only contribute to our knowledge of the physiologic processes involved in the mechanism of milk secretion, but also give significant leads to the clinician who directs the care of breast-fed infants. They emphasize a real need for detailed controlled and coordinated studies on the blood, urine and milk of women in relation to sociologic and psychologic factors—studies that are now in progress in these laboratories.

CONCLUSIONS

The variations that occur in the composition of human milk at periodic four hour intervals throughout the day and night have been studied. The subjects were three women living in their usual home environments, typical of the average middle-class American family. Under the conditions of these experiments it was demonstrated that, independently of variations in such factors as food, rest, activity, stage of lactation, climate and possible errors involved in the methods followed, there were significant changes during the day in the volume of the breast milk of the three women, and characteristic daily trends in the variation in composition of the milk with respect to the fat, total solids, total nitrogen, total ash, calcium, phosphorus and chloride components.

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33. Fiske, C. H.: Inorganic Phosphate and Acid Excretion in the Postabsorptive Period, J. Biol. Chem. **49**:171, 1921. Campbell, J. A., and Webster, T. A.: Day and Night Urine During Complete Rest, Laboratory Routine, Light Muscular Work and Oxygen Administration, Biochem. J. **15**:660, 1921.

34. Kleitman, N.: Studies on the Physiology of Sleep: I. The Effect of Prolonged Sleeplessness on Man, Am. J. Physiol. **66**:67, 1923. Simpson, G. E.: Changes in the Composition of Urine Brought About by Sleep and Other Factors, J. Biol. Chem. **84**:393, 1929.

35. Campbell and Webster (footnote 33).

THE RESPIRATORY METABOLISM IN INFANCY AND IN CHILDHOOD

XIII. THE CALORIGENIC ACTION OF THYROID EXTRACTS IN NORMAL INFANTS *

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Experimental evidence and clinical experience have fully established the calorifacient action of thyroid substance in thyroidectomized animals and in man with hypothyroidism. Published studies of normal animals [1] and of men and women without hypothyroidism [2] are not as conclusive,

* Submitted for publication, July 21, 1931.

* From the Department of Pediatrics, Cornell University Medical College and the New York Nursery and Child's Hospital.

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but in general they tend to show that the drug induces a similar but less constant response in these subjects. To our knowledge, the literature contains few references to similar metabolic studies in infants and children without hypothyroidism.[3] Such investigations should be of physiologic interest and of clinical assistance in appraising the rôle of thyroid therapy in these subjects in other than hypothyroid states.

Another phase of the thyroid problem that merits further study relates to the relative potency of the different commercial preparations in common use. At the present time, the drug is officially standardized according to its iodine content. This method of standardization was adopted chiefly as a result of experimental studies by Hunt[4] on the resistance of white mice to acetonitrile, together with published evidence bearing on loss of weight and nitrogen excretion,[5] on the rate of meta-

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morphosis of tadpoles and salamanders,[6] on the effect on growth and organ hypertrophy in young animals [7] and on the relative toxicity of different thyroid products.[8] We know of no systematic studies that correlate the potency of thyroid extracts with their iodine content as tested directly by their calorifacient effect in human subjects.

This investigation includes a report of the physiologic action of thyroid extracts in normal infants and an evaluation of the calorigenic potency of several commercial preparations of thyroid which are in general use. In addition, attention will be directed to the clinical implications suggested by the physiologic and pharmacologic data.

MATERIAL AND METHODS

Subjects.—The series comprised seven infants from 1 to 16 months of age, in various states of nutrition and with presumably normally active thyroid glands as revealed by their basal metabolic rates. Two of the infants were markedly emaciated; three, moderately undernourished, and the remaining two, well nourished (table 1). Two of the subjects (E. K. and H. B.) were girls; the others, boys. They were all afebrile (with two exceptions, table 2) and free from acute infections and alimentary disturbances during the periods of observation of from one to three months. Detailed data of the nutritional status of the subjects are presented in table 1.

Methods of Study.—A closed circuit apparatus of the Benedict-Talbot type [9] was employed to measure the energy metabolism. The apparatus, technic of mea-

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TABLE 1.—*Nutritional Status of Infants*

	Date	Weight, Kg.	Height, Cm.	Surface Area,* Sq.M.
F. S.	10/24/30	5.90	67.5	0.322
Born 3/2/30	11/ 2/30	6.07	67.5	0.328
	11/17/30	6.25	68.3	0.336
	12/ 8/30	6.39	70.0	0.345
	12/24/30	6.45	70.0	0.345
	12/31/30	6.66	70.5	0.353
	1/16/31	6.65	70.5	0.353
	1/26/31	7.27	71.0	0.368
E. K.	10/27/30	3.64	52.5	0.220
Born 9/30/30†	11/ 7/30	4.00	53.0	0.230
	11/17/30	4.09	54.5	0.239
	12/12/30	4.72	56.0	0.258
	12/23/30	4.70	56.5	0.260
	1/ 2/31	4.60	57.5	0.260
	1/14/31	4.93	57.5	0.268
H. B.	11/16/30	7.10	73.0	0.372
Born 4/7/30†	11/28/30	7.15	73.0	0.373
	12/10/30	7.10	73.5	0.373
	12/11/30	7.06	73.5	0.372
	12/17/30	7.15	74.0	0.376
J. S.	11/ 3/30	8.13	74.5	0.399
Born 10/31/29	11/10/30	8.48	74.5	0.410
	12/ 3/30	8.58	75.5	0.415
	12/15/30	8.84	75.5	0.420
	2/18/31	9.46	77.0	0.437
	2/27/31	9.59	77.5	0.441
	3/ 6/31	9.72	77.5	0.442
	3/14/31	9.74	78.0	0.443
	3/26/31	10.25	79.0	0.460
R. G.	1/22/31	4.46	63.5	0.276
Born 8/20/30	2/ 2/31	4.85	63.5	0.287
	2/16/31	4.73	65.5	0.290
	2/20/31	4.66	65.5	0.288
	2/23/31	4.69	65.5	0.289
	2/25/31	4.66	65.5	0.288
	2/27/31	4.72	65.5	0.289
	3/ 7/31	4.55	66.0	0.284
	3/13/31	4.43	66.0	0.283
	3/16/31	4.55	66.0	0.284
	3/20/31	4.55	66.0	0.284
	3/23/31	4.55	66.0	0.284
	3/27/31	4.52	66.5	0.284
	4/ 1/31	4.52	66.5	0.284
	4/ 7/31	4.74	66.5	0.292
	4/13/31	4.74	66.5	0.292
	4/15/31	4.66	66.5	0.291
F. W.	2/ 6/31	4.43	60.5	0.266
Born 9/20/30	2/17/31	4.55	62.0	0.272
	2/20/31	4.57	62.0	0.272
	2/23/31	4.65	62.0	0.276
	2/28/31	4.87	62.5	0.283
	3/ 9/31	4.69	63.3	0.281
	3/18/31	4.83	64.5	0.289
	3/20/31	4.84	64.5	0.289
	3/25/31	5.02	65.0	0.295
	3/26/31	4.89	65.0	0.290
	4/ 1/31	5.04	65.0	0.294
	4/ 7/31	5.17	65.0	0.297
	4/16/31	5.29	66.5	0.305
F. Wi.	3/ 4/31	6.68	68.5	0.345
Born 5/2/30	3/11/31	6.55	69.0	0.342
	3/17/31	6.34	69.5	0.341
	4/ 2/31	6.66	70.5	0.350

* Derived from nomogram by R. R. Hannon for estimating surface area of children according to the formula of Du Bois and Du Bois, in Du Bois, E. F.: Basal Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1927, p. 124.

† Girls; the remaining subjects were boys.

surements and methods of calculation were fully described in earlier papers of this series.[10] Sixty-three observations of from one to three hours were made up on the seven infants preceding, during and following the oral administration of various thyroid preparations.[11] Ingestion of the thyroid extracts was invariably achieved without losses. The glandular products were given in daily amounts ranging from 1 to 15 grains (0.06 to 1 Gm.) for from one to three weeks. The dosage of thyroxine was maintained at the uniform level of 1 mg. daily for one week. These amounts were preferred to the smaller dosages usually effective in cretinism since they correspond more closely to the dosage employed in a number of reported studies of normal adults.[12] All factors such as activity, diet, body and environmental temperature, humidity and clothing, which are known to influence the energy metabolism were in so far as possible eliminated, and observations on each infant were made under strictly comparable conditions.

Following one or more control observations of the basal metabolism, each infant received a course of medication with one of the thyroid preparations (table 2). When the metabolic rate had attained a maximum level, the medication was discontinued and measurements of the metabolism were repeated at intervals of several days until the rate approximated the initial basal level. The same procedure was duplicated in most instances during medication with the other thyroid products and following withdrawal of the drugs. The calorimetric data and the amounts of the drugs administered to the different infants are given in table 2.

Alcohol Checks.—As is our custom, the accuracy of the experimental technic was controlled by frequent alcohol checks, the details of which appear in table 3. The apparatus measured the carbon dioxide with an average error of —0.6 per cent and with a maximum error of —3.6 per cent on July 2. The average error in the measurement of oxygen, on which the heat production is based, was —1 per cent, the maximum error being —4.2 per cent, also on July 2. The respiratory quotient averaged 0.671 for the entire series and ranged between 0.663 and 0.680 in individual observations, as against the theoretic quotient of 0.667. The alcohol checks and the consistent results obtained in duplicate observations on the same infant on different days (deviations of less than ± 5 per cent) establish the probable experimental error of the method below ±5 per cent.

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TABLE 2.—*Calorimetric Data in Terms of Averages per Hour* *

Subject	Date	Duration of Observation, Min.	Water, Gm.	Carbon Dioxide, Gm.	Oxygen, Gm.	Respiratory Quotient	Calories†	Temperature Rectal F., Average	Temperature Chamber C., Average	Thyroid Dosage ‡
F. S.	10/24	135	8.64	6.17	4.96	0.905	17.01	99.2	25.7	Basal
	11/ 2	120	6.96	6.22	5.00	0.904	17.10	98.7	24.6	Whole gland: 1½ grains, 4 days; 2½ grains, 1 day; 3 grains, 4 days
	11/17	100	14.06	7.18	5.56	0.917	19.84	99.2	26.4	Whole gland: 5 grains, 2 days; 7½ grains, 2 days; 10 grains, 10 days
	12/ 8	120	10.72	6.70	5.45	0.879	18.56	98.6	25.1	No thyroid; 21 days
	12/24	120	12.78	7.96	7.06	0.820	23.69	98.8	24.5	Desiccated extract: 10 grains, 8 days
	12/31	120	9.07	6.85	5.57	0.894	19.05	98.6	24.1	No thyroid: 7 days
	1/16	120	11.05	8.20	6.98	0.854	23.63	99.5	23.4	Desiccated extract: 10 grains, 10 days
	1/26	90	10.33	7.27	6.25	0.846	21.12	98.1	23.1	No thyroid: 8 days
E. K.	10/27	150	.....	2.96	2.48	0.867	8.42	98.6	26.4	Basal
	11/ 7	120	.....	3.63	3.03	0.871	10.30	98.2	24.7	Whole gland: 1 grain, 3 days; 2 grains, 2 days; 4 grains, 2 days
	11/17	90	.....	3.67	3.01	0.885	10.27	99.0	25.2	Whole gland: 6 grains, 6 days; 8 grains, 4 days
	12/12	120	7.12	4.40	3.43	0.933	11.85	98.3	25.1	No thyroid: 24 days
	12/23	120	7.37	4.25	3.39	0.912	11.64	97.8	25.8	No thyroid: 35 days
	1/ 2	90	6.30	4.90	4.05	0.884	13.82	98.1	24.6	Desiccated extract: 8 grains, 8 days
	1/14	120	6.81	4.42	3.57	0.902	12.23	97.9	25.5	No thyroid: 11 days
H. B.	11/16	95	10.08	6.26	5.62	0.812	18.83	98.8	24.5	Basal
	11/28	120	8.98	6.88	5.91	0.847	19.97	99.7	25.0	Desiccated extract: 1 grain, 1 day; 2 grains, 2 days; 4 grains, 5 days
	12/10	60	14.48	8.02	7.41	0.787	24.66	99.3	25.5	Desiccated extract: 7 grains, 1 day; 10 grains, 11 days
	12/11	180	10.63	8.09	7.26	0.815	24.20	98.9	25.4	Desiccated extract: 10 grains, 12 days
	12/17	105	9.60	7.24	6.38	0.828	21.45	99.1	24.6	No thyroid: 7 days
J. S.	11/ 3	90	10.71	6.61	6.27	0.766	20.75	99.8	25.1	Basal
	11/10	105	12.00	7.18	6.13	0.852	20.74	98.6	25.4	Basal
	12/ 3	120	10.73	7.74	6.67	0.844	22.52	98.2	24.9	Whole gland: 3 grains, 1 day; 4½ grains, 12 days; 8 grains, 3 days; 12 grains, 5 days
	12/15	90	11.48	10.08	8.70	0.843	29.37	100.8	24.8	Thyroxine: 1 mg., 4 days; last dose 12/13
	2/18	75	.....	8.34	7.28	0.835	24.53	99.3	25.6	Basal
	2/27	135	.....	9.58	8.18	0.852	27.68	99.1	24.9	Whole gland: 15 grains, 7 days
	3/ 6	105	.....	8.55	7.64	0.814	25.60	98.9	25.2	No thyroid: 7 days
	3/14	91	19.02	10.95	9.07	0.879	30.90	99.8	25.6	Desiccated extract: 15 grains, 8 days
	3/26	90	.....	8.15	6.92	0.866	23.39	97.4	25.5	No thyroid: 11 days

F. Wi.	3/ 4	45	11.12	7.04	6.11	0.838	20.60	99.1	24.2	Basal
	3/11	135	11.55	7.95	6.52	0.886	22.25	99.2	24.0	Desiccated extract: 10 grains, 5 days
	3/17	90	13.29	7.95	6.57	0.880	22.39	99.4	23.6	Desiccated extract: 10 grains, 11 days
	4/ 2	90	13.71	6.93	....	§	19.59	98.6	25.2	No thyroid: 15 days,
R. G.	1/22	90	7.28	4.08	3.81	0.780	12.66	99.9	25.2	Basal
	2/ 2	90	7.13	4.84	4.00	0.880	13.63	97.8	23.5	Basal
	2/16	90	7.89	5.63	4.92	0.833	16.57	98.2	24.0	Whole gland: 10 grains, 7 days
	2/20	90	9.61	5.50	4.65	0.860	15.76	98.3	24.3	No thyroid: 2 days
	2/23	90	7.26	5.43	4.44	0.889	15.16	98.4	25.1	No thyroid: 5 days
	2/25	120	7.28	5.14	4.29	0.872	14.59	98.4	24.9	No thyroid: 7 days
	2/27	90	7.53	5.28	4.43	0.866	15.04	99.0	24.3	No thyroid, 9 days
	3/ 7	100	10.19	6.40	5.26	0.885	17.95	99.0	24.7	Desiccated extract: 10 grains, 8 days
	3/13	90	11.81	6.12	5.17	0.861	17.53	99.3	25.1	No thyroid, 4 days
	3/16	75	7.89	5.38	4.64	0.844	15.67	98.0	24.8	No thyroid: 7 days
	3/20	90	8.76	5.11	....	§	14.67	97.2	25.7	No thyroid: 11 days
	3/23	90	7.34	5.88	....	§	16.88	98.9	25.1	Thyroxine: 1 mg., 3 days
	3/27	120	12.45	6.41	5.19	0.902	17.78	98.6	26.5	Thyroxine: 1 mg., 7 days
	4/ 1	90	9.18	5.73	4.96	0.841	16.74	97.9	24.6	No thyroxine: 5 days
	4/ 7	120	7.68	6.10	....	§	17.51	98.8	24.1	No thyroxine: 11 days
	4/13	75	7.28	5.37	4.72	0.827	15.87	97.4	25.0	No thyroxine: 17 days
	4/15	90	8.12	5.11	4.41	0.842	14.89	97.6	25.4	No thyroxine: 19 days
F. W.	2/ 6	90	6.60	5.17	4.33	0.870	14.72	98.3	24.1	Basal
	2/17	91	7.58	6.18	5.14	0.875	17.49	98.3	25.2	Whole gland: 2 grains, 1 day; 10 grains, 7 days
	2/20	90	10.03	6.64	5.55	0.871	18.87	98.9	25.2	No thyroid: 1½ days
	2/23	90	9.53	6.20	5.15	0.875	16.74	98.9	26.0	No thyroid: 4½ days
	2/28	120	5.62	5.80	4.54	0.930	15.67	98.5	24.5	No thyroid: 9 days
	3/ 9	120	7.61	8.01	6.61	0.882	22.54	101.5	24.1	Desiccated extract: 2 grains, 1 day; 10 grains, 7 days
	3/18	91	7.85	6.05	5.04	0.873	17.14	98.8	26.1	No thyroid: 8 days
	3/20	120	7.97	5.89	....	§	16.77	98.1	25.6	No thyroid: 10 days
	3/25	120	.....	8.28	....	§	24.12	99.6	26.1	Thyroxine: 1 mg., 5 days
	3/26	60	16.33	8.41	7.20	0.850	24.35	99.5	24.8	Thyroxine: 1 mg., 6 days
	4/ 1	90	10.54	6.81	....	§	19.39	99.7	24.1	No thyroxine: 6½ days
	4/ 7	120	9.31	6.02	4.78	0.916	16.43	98.3	23.0	No thyroxine: 13 days
	4/16	135	9.21	6.42	5.14	0.909	17.64	98.8	25.5	No thyroxine: 25 days

* All observations were made during sleep. Identical meals were given to each infant preceding determinations, and the time interval between the meals and the onset of observations was approximately the same in every instance.

† The nitrogen in the urine was not determined. Heat production was calculated on the assumption that 15 per cent of the calories were derived from the combustion of protein.

‡ The thyroid products were administered by mouth.

§ A leak occurred in the oxygen cylinder. The respiratory quotients were assumed to be the same as those obtained in observations under comparable conditions. In these determinations, the heat production was calculated from the carbon dioxide.

TABLE 3.—*Alcohol Checks for Experimental Year (1930-1931)*

Date	Minutes	Alcohol, Gm.	Water			Carbon Dioxide			Oxygen			Respiratory Quotient (0.667)		Heat
			Theory, Gm.	Found, Gm.	Error, per Cent	Theory, Gm.	Found, Gm.	Error, per Cent	Theory, Gm.	Found, Gm.	Error, per Cent	Found, Gm.	Error	Theory, Calories
July 2	60			7.30			8.59			9.34		0.669		
	60			6.61			8.03			8.59		0.679		
	30			3.64			4.38			4.81		0.662		
Average per hour		4.60	6.10	7.02	+15.1	8.78	8.46	— 3.6	9.58	9.18	— 4.2	0.670	+0.003	32.55
October 17	50			5.40			7.60			7.93		0.697		
	45			3.54			5.29			5.58		0.688		
	40			4.62			6.44			7.22		0.649		
Average per hour		4.46	5.91	6.03	+ 2.0	8.52	8.61	+ 1.1	9.30	9.26	0.0	0.678	+0.011	31.57
October 20	60			7.58			9.96			10.68		0.678		
	63			7.97			10.46			11.51		0.661		
	31			3.33			4.84			5.16		0.682		
Average per hour		5.04	6.68	7.38	+10.5	9.64	9.79	+ 1.6	10.51	10.66	+ 1.4	0.672	+0.005	35.70
November 19	45			4.14			5.75			6.02		0.695		
	45			4.26			6.23			6.71		0.675		
	60			5.37			7.95			8.57		0.675		
Average per hour		4.03	5.35	5.51	+ 3.0	7.71	7.97	+ 3.4	8.41	8.52	+ 1.3	0.680	+0.013	28.56
January 6	60			6.44			9.42			10.40		0.659		
	60			6.21			9.10			9.90		0.669		
Average per hour		4.78	6.34	6.33	0.0	9.13	9.26	+ 1.4	9.96	10.15	+ 1.9	0.664	—0.003	33.84
January 17	60			5.91			8.49			9.34		0.660		
	60			5.90			8.71			9.54		0.664		
Average per hour		4.59	5.72	5.91	+ 3.3	8.78	8.60	— 2.1	9.58	9.44	— 1.5	0.663	—0.004	32.52
March 5	35			4.20			6.29			6.78		0.675		
	45			4.43			6.62			7.44		0.647		
	45			4.20			6.34			6.66		0.692		
Average per hour		4.95	6.16	6.16	0.0	9.46	9.24	— 2.3	10.32	10.02	— 2.9	0.671	+0.004	35.05
March 26	45			5.51			8.27			8.96		0.671		
	45			5.70			8.52			9.33		0.664		
Average per hour		6.00	7.47	7.47	0.0	11.46	11.19	— 2.3	12.51	12.19	— 2.5	0.668	+0.001	42.50
April 10	45			4.11			6.11			6.58		0.675		
	45			4.02			6.04			6.51		0.675		
Average per hour		4.32	5.37	5.42	+ 0.9	8.25	8.10	— 1.7	9.00	8.73	— 3.0	0.675	+0.008	30.57
Total average			55.10	57.23	+ 3.9	81.73	81.22	— 0.6	89.17	88.15	— 1.1	0.671	+0.004	33.65

RESULTS

The results, although interrelated, may be grouped conveniently into two main divisions and several subdivisions as follows:

1. The physiologic response of normal infants to thyroid therapy
   (*a*) Calorigenic effects
   (*b*) Persistence of action
   (*c*) Clinical response
2. The calorigenic potency of thyroid extracts
   (*a*) In terms of absolute dosage
   (*b*) In terms of iodine content

THE PHYSIOLOGIC RESPONSE OF NORMAL INFANTS TO THYROID THERAPY

Calorigenic Effect.—For comparative purposes, the energy metabolism calculated as calories per twenty-four hours was referred to the

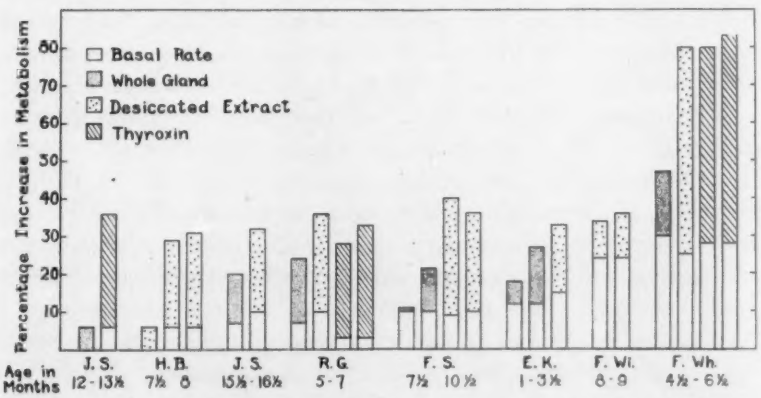

Chart 1.—The calorigenic effect of thyroid extracts in infants without hypothyroidism. Each column represents two metabolic measurements; the control basal rate and the percentage increase above the basal level as the result of medication.

recently published basal standards for infants based on the two physical factors, body weight and body stature.[13] Although these standards were selected for comparison, it may be stated that substitution of the generally accepted basal standards referred to any of the single characteristics, age, weight, height or surface area,[14] did not affect the

13. Levine, S. Z., and Marples, E.: The Respiratory Metabolism in Infancy and in Childhood: XII. A Biometric Study of Basal Metabolism in Normal Infants, Am. J. Dis. Child. **41**:1332 (June) 1931.

14. (*a*) Benedict, F. G., and Talbot, F. B.: Metabolism and Growth from Birth to Puberty, pub. no. 302, Carnegie Inst., Washington, 1921. (*b*) Benedict, F. G.: Energy Requirements from Birth to Puberty, Boston M. & S. J. **181**:107 (July 31) 1919. (*c*) Benedict, F. G.: Physical Factors in Predicting the Basal Metabolism of Girls, Proc. Am. Philos. Soc. **63**:25, 1924. (*d*) Talbot, F. B.: Basal Metabolism of Children, Physiol. Rev. **5**:477 (Oct.) 1925.

results. The results for each infant before and during the administration of thyroid, expressed as percentage deviation from the foregoing basal standards, are graphically shown in chart 1. Each column represents two metabolic measurements; one preceding and one during treatment.

The initially normal or elevated basal rates of the infants is satisfactory evidence that they were all endowed with presumably normal thyroid glands. The high basal levels of two of the subjects (F. Wi. and F. Wh.) are undoubtedly ascribable to their severe undernutrition and to the presence in their organisms of a relative excess of active protoplasmic tissue.[15] The slight variations in the control basal rates of several of the infants are due to an insufficient time interval between courses of medication which in some instances permitted only an approximate return to the original basal rate.

The stimulation of metabolism induced by thyroid therapy ranged between 1 and 52 per cent above the respective basal levels of the different infants. The increments of increase (10 per cent and more) notably exceeded the probable experimental error of the method (± 5 per cent) in twenty of the twenty-four pairs of observations shown in chart 1. In the four instances in which the results cannot with certainty be considered significant (one observation on J. S., H. B., F. S. and E. K.), the metabolic measurements were made within five days or less following institution of treatment with the whole gland product in relatively small dosage (except for H. B. who received the desiccated extract, table 2).

With these exceptions, the infants responded to all forms of thyroid therapy in the dosages given (table 2) with a significant but variable augmentation of their energy metabolism. In the few infants who were studied during the period of rising heat production, the maximum level was always attained within ten days following the onset of medication. This time interval of maximum stimulation coincides with that reported for normal animals,[16] adults without hypothyroidism[17] and myxedematous patients,[18] and suggests that the four infants who did not react significantly to the administration of thyroid might have responded more markedly if treatment had been prolonged for several additional days.

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15. Levine, S. Z.; Wilson, J. R., and Gottschall, F.: The Respiratory Metabolism in Infancy and in Childhood: VIII. The Respiratory Exchange in Marasmus: Basal Metabolism, Am. J. Dis. Child. **35**:615 (April) 1928.

16. Footnote 1, *h*, *j* and *l*.

17. Footnote 2, *h* and *k*.

18. (*a*) Boothby, W. M., and Sandiford, I.: Basal Metabolism, Physiol. Rev. **4**:69 (Jan.) 1924. (*b*) Plummer, H. S.: Interrelationship of Function of the Thyroid Gland and of Its Active Agent, Thyroxin, in the Tissues of the Body. J. A. M. A. **77**:243 (July 21) 1921.

The metabolic response of the different infants to the administration of thyroid was apparently unrelated to the original level of their basal rates. For example, the rise in metabolism of R. G. and F. Wh. whose initial basal rates differed markedly (+7 and +25 per cent) was precisely the same, being 17 per cent above the respective basal levels in both instances following equivalent amounts of the whole gland product. Similarly, the metabolism of H. B. and F. S. whose initial basal rates were essentially the same (+6 and +9 per cent) rose 23 and 31 per cent above their respective basal levels following similar amounts of the desiccated extract. This lack of correlation between the basal level and the calorigenic action of the drug has already been demonstrated for myxedematous adults by Boothby.[19]

The calorifacient capacity of artificially administered thyroid extracts seems rather to depend on other intrinsic and extraneous factors, some of which were uncontrollable in this study. Among the intrinsic and uncontrollable variables may be included body size, variable absorption from the gastro-intestinal tract following oral administration of the drug and individual susceptibility to the drug depending in part at least on the varying activity of the intact thyroid glands of the several infants. The extrinsic variables include chiefly the duration of administration and the dosage and potency of the thyroid preparations used. Some of these factors have been or will be considered in greater detail in a later section.

At this point, we wish merely to emphasize the marked similarity in the metabolic response of normal infants and of normal adults to thyroid medication. In adequate dosage, both groups react to the drug with an elevated energy metabolism and often with clinical symptoms simulating hyperthyroidism.[20] Similarly, although relatively few infants were studied with smaller dosage (table 2 and unpublished data), the consistent results and the abundant evidence in the literature indicate that subjects of all ages without hypothyroidism either fail to react or react less markedly both metabolically and clinically to amounts of thyroid which are invariably effective in cretinism and myxedema.[21]

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19. Boothby, W. M.: The Basal Metabolic Rate in Hyperthyroidism, J. A. M. A. **77**:252 (July 23) 1921.

20. Footnote 2, *a*, *e*, *j* and *k*.

21. (*a*) Boothby, W. M.; Sandiford, I.; Sandiford, K., and Slosse, J.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects, Tr. A. Am. Physicians **40**:195, 1925. (*b*) Means, J. H., and Aub, J. C.: The Basal Metabolism in Hypothyroidism, Arch. Int. Med. **24**:404 (Oct.) 1919. (*c*) Janney, W. W.: Studies in Thyroid Therapy, Arch. Int. Med. **22**:187 (Aug.) 1918. (*d*) Talbot, F. B., and Moriarity, M. E.: The Value of Basal Metabolism in the Diagnosis and Treatment of Cretinism, Am. J. Dis. Child. **25**:185 (March) 1923. (*e*) Talbot, F.; Sollgruber, K., and Hendry, M.: Calorimetrische Untersuchungen an kindlichen Kretinin, Ztschr. f. Kinderh. **37**:98, 1924.

The intensity of reaction to equivalent amounts of thyroid above the minimum effective dosage for normal subjects is usually less than in persons with hypothyroidism.[22] The hypothesis evolved to explain this disparity of response in persons with and without hypothyroidism is reserved for later consideration.

The intermediary metabolism of the foodstuffs, protein, carbohydrate and fat was not consistently influenced by the administration of thyroid extracts as indicated by the respiratory quotients and by the nitrogen excretion in the urine. The latter data will appear in a subsequent communication.[23] The quotients remained either at approximately the same levels as prior to medication, or when they varied, the deviations below and above the original levels were equally frequent (table 2). The results in these normal infants, showing that the increased expenditure of energy resulting from this form of treatment is usually at the expense of all three food elements, are in accord with the results reported in adults.[24]

Persistence of Thyroid Action.—The course of the energy metabolism following cessation of thyroid medication is illustrated in chart 2.

The heat production of all of the infants gradually fell and usually returned to, or even dropped below, the original basal level within a period of from one to two weeks. The fall in metabolism was invariably accompanied by a disappearance of clinical symptoms. In one instance only (E. K., not recorded in the chart), the metabolism had not as yet returned to the original basal level thirty-five days following withdrawal of the drug. The rapidity of decline varied in the different infants and did not seem to depend on the height of the energy metabolism at the time of omission of medication. The usual persistence of thyroid action in these infants without hypothyroidism closely parallels

22. (*a*) Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: The Calorigenic Action of Thyroxin at Different Levels of Basal Metabolism in Myxedema, J. Clin. Investigation **7**:437 (Aug.) 1919. (*b*) Thompson, W. O.: Studies of Blood Volume: I. The Blood Volume in Myxedema with a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema, ibid. **2**:477 (Aug.) 1926.

23. Weymuller, L. E.; Wyatt, T. C.; Levine, S. Z., and Marples, E.: The Respiratory Metabolism in Infancy and in Childhood: XIV. Thyroid Therapy and Protein Metabolism in Normal Infants, to be published.

24. Footnote 21 *a*. (*a*) Grafe, E.: Die pathologische Physiologie des Gesamt-Stoff-und Kraftwechsels bei der Ernährung der Menschen, Ergebn. d. Physiol. **21**: 242, 1923. (*b*) Deuel, J. H.; Sandiford, I.; Sandiford, K., and Boothby, W. M.: The Effect of Thyroxin on the Respiratory and Nitrogen Metabolism of a Normal Subject Following Nitrogen-Free Diet, J. Biol. Chem. **76**:407 (Feb.) 1928. (*c*) Boothby, W. M., and Sandiford, I.: The Total and Nitrogenous Metabolism in Exophthalmic Goitre, J. A. M. A. **81**:795 (Sept. 8) 1923. (*d*) Du Bois, E. F.: Clinical Calorimetry: XIV. Metabolism in Exophthalmic Goiter, Arch. Int. Med. **17**:915 (June) 1916.

the results obtained by investigators working with normal animals [16] and with adults without hypothyroidism [25] and is of considerably shorter duration than those reported for subjects with hypothyroidism. Plummer, Boothby and other workers [26] were able to demonstrate the persistence of thyroid action in myxedematous patients and in thyroidectomized animals for as long as from six to ten weeks following omission of medication. Especially significant in this connection are the observations of Thompson and his collaborators.[27] They found that the return to basal levels of two myxedematous patients required eighty and eighty-five days following omission of thyroid therapy when the initial rates were at myxedematous levels and only eighteen and nine-

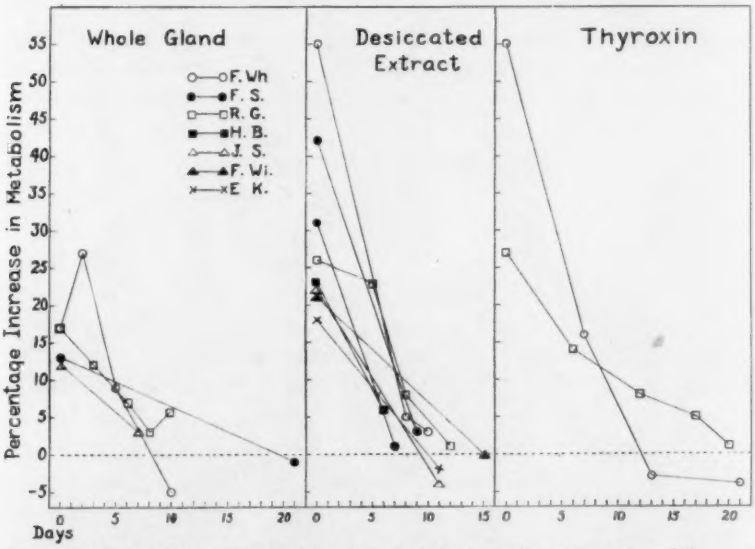

Chart 2.—Persistence of thyroid action in infants without hypothyroidism. The metabolic level of each infant at the time of omission of medication is shown.

teen days when the initial basal rates were at normal levels as the result of prior treatment.

The parallel duration of thyroid action in infants and in adults with and without hypothyroidism affords additional evidence of the similarity of the metabolic response of all subjects, irrespective of age.

Clinical Response.—Coincident with the elevated metabolic rate accompanying thyroid therapy, a number of the infants developed clinical symptoms which closely simulated spontaneous hyperthyroidism. These symptoms which were manifested in varying severity in the dif-

25. Footnotes 12 *a* and 21 *a*.
26. Footnote 2 *h* and *i*.
27. Footnote 22 *a*.

ferent infants included stationary or declining body weight, accelerated heart rate, the frequent appearance of a generalized eruption resembling miliaria and occasionally fever. The eruption is ascribed by many authors to the presence of iodine in the drug. In no instance did exophthalmos develop. The following points are of interest clinically and should be stressed. Toxic manifestations were never apparent with small dosages of the drug; the severity of symptoms when present did not necessarily parallel the calorigenic action; toxic symptoms were not an inevitable accompaniment of even high dosage; and finally, the appearance of toxic manifestations was always preceded for a variable but appreciable period by a well sustained elevation of the energy metabolism.

The minimum dosage capable of provoking toxic symptoms in these normal infants appreciably exceeded the threshold of dosage usually necessary to induce the same effects in cretins.[28] This disparity of clinical as well as of metabolic response in the two groups is in accord with the idea promulgated by Thompson working with adults,[29] that the reaction to thyroid is the single most important criterion for determining underfunction of the thyroid gland. In accordance with this idea, the suggestion is advanced that the reaction to thyroid may possibly be utilized in the clinic as a therapeutic test for differentiating the mental and physical retardation in infants (and also in adults) due to thyroid hypofunction from that due to other anomalies. When direct measurements of the energy exchange are not feasible, a profound clinical reaction of a retarded infant to thyroid in dosages of 2 to 3 grains (0.13 to 0.19 Gm.) of the desiccated extract or of 5 to 7.5 grains (0.32 to 0.49 Gm.) of the whole gland daily is presumptive evidence that the retardation is ascribable to thyroid hypofunction. Similarly, the absence of symptoms following such medication may imply that the condition is not hypothyroidism. Work is in progress at present to test the validity of this suggestion. In this connection, it is of interest to mention that Aub and Stern[30] were able to give an adult patient with heart block from 26 to 28 grains (1.7 to 1.8 Gm.) of the desiccated extract for six weeks without the appearance of clinical symptoms.

THE CALORIGENIC POTENCY OF THYROID EXTRACTS

The study as planned, afforded the opportunity of comparing in the same group of infants the metabolic response induced by whole thyroid gland, the desiccated extract and synthetic thyroxine. The data were,

28. Footnotes 3 *a* and 21 *d* and *e*.

29. Footnote 22 *a*. Thompson, W. O., and Thompson, P. K.: Low Basal Metabolism: II. Permanent Type Without Myxedema, J. Clin. Investigation **5**: 471 (April) 1928.

30. Footnote 12 *a*.

therefore, suitable for assaying by metabolic methods the relative potency of the three products.

In Terms of Absolute Dosage.—To eliminate the variable factors of dosage and body size, the daily intake of thyroid by the various infants was calculated in terms of 1 grain (0.065 Gm.) per square meter of body surface. The percentage increase above the respective basal levels of the different infants following this calculated dosage of two of the thyroid products (whole gland and desiccated extract) is graphically shown in chart 3.

The calorigenic potency of the desiccated extract is seen to be invariably of a higher order than that of the whole gland product in equivalent dosage. As might be expected from the conditions of observations, the response of individual infants to both forms of therapy

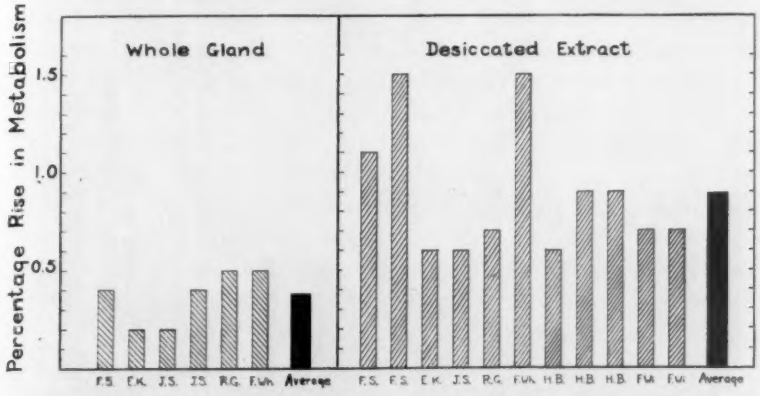

Chart 3.—The calorigenic effect of whole thyroid gland and of desiccated extract in terms of absolute dosage. The results are expressed as percentage increase above the basal levels, calculated on the basis of a uniform intake of 1 grain (0.065 Gm.) of thyroid per square meter of body surface.

varied; the increments of metabolic increase per grain per square meter ranged from 0.1 to 0.6 per cent with the whole gland, and from 0.6 to 1.5 per cent with the desiccated extract. As previously stated, the two factors which undoubtedly explain in part at least these individual variations are variable absorption of the drug from the gastro-intestinal tract following oral administration and varying activity of the thyroid glands of the different infants. The ideal procedure to eliminate these variables would obviously involve the parenteral administration of the drug to thyroidless persons, but these conditions are difficult to attain during infancy. It must be emphasized that the limitations of our method and the individual variations cannot be minimized, but a comparison of the average results secured in all of the infants with the two forms of the drug is of considerable interest. The rise in metabolism

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for the entire series of infants following whole gland and desiccated extract per grain per square meter averaged 0.38 and 0.89 per cent, respectively. The average potency of the desiccated product was, therefore, 2.34 times that of the whole gland as judged by their relative effects on the energy exchange of our infants. This ratio of potency, estimated metabolically, is especially interesting when one learns that the iodine content of the desiccated extract is 2.5 times that of the whole gland as reported by the manufacturers. It therefore seemed of interest to determine the metabolic response of the infants to the different thyroid preparations in equivalent iodine dosage rather than in terms of absolute quantities and to include thyroxine in the comparison. The results of this calculation appear in graphic form in chart 4.

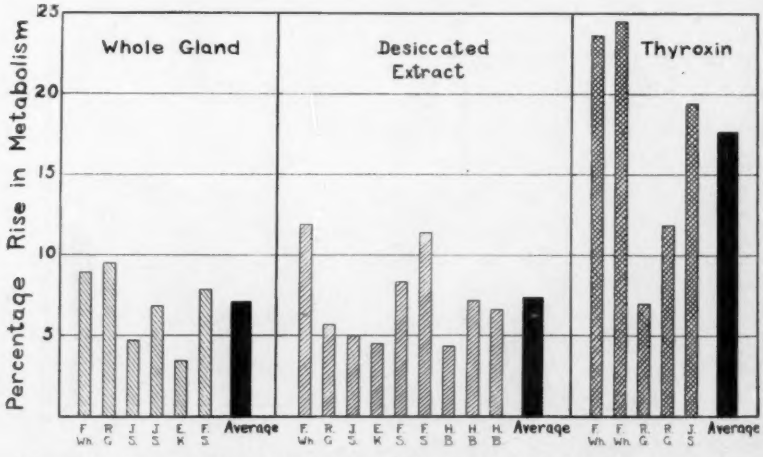

Chart 4.—The calorigenic effect of whole thyroid gland, desiccated extract and thyroxine in terms of iodine content. The results are expressed as percentage increase above the basal levels calculated on the basis of a uniform intake of 1 mg. of iodine per square meter of body surface.

In Terms of Iodine Content.—A similar method of calculation was employed in this as in the preceding chart, the only difference being the standard unit of dosage which was used in the two instances.

As in the preceding chart and for the reasons previously mentioned, the response of individual infants to the glandular products in equi-iodine amounts also varied, but the noteworthy fact is that the respective increments of increase per milligram of iodine per square meter fol-

31. Analyses of the iodine content made by the manufacturers were accepted. As reported, the whole gland contained the equivalent of 0.4 per cent iodine in the desiccated substance (or 0.0008 grain of iodine per one grain tablets); the desiccated extract, 0.2 per cent (or 0.002 grain per one grain tablets); the thyroxine, 65 per cent of iodine.

lowing whole gland and desiccated extract averaged 7.07 and 7.33 per cent. The parallel results strongly suggest that the potency of thyroid products, estimated metabolically, is closely related to their iodine content held in organic combination. The results are consistent with the conclusions of Reid Hunt based on the acetonitrile test and with other experimental studies in animals.[32] On the other hand, the active principle of thyroid, thyroxine, which contains 65 per cent of its molecule as iodine, exerted a more profound influence on the metabolism of the infants than either of the two glandular products. The increment of increase following the administration of thyroxine averaged 17.62 per cent per milligram of iodine per square meter as against approximately 7 per cent for glandular extracts. In other words, the calorifacient capacity of thyroxine which contains 325 and 812.5 times as much iodine by weight as the desiccated extract and whole gland, respectively,[31] was between 700 and 1,400 times that of the former and between 1,000 and 2,000 times that of the latter product in the three infants (J. S., R. G. and F. Wh.) who were studied with all three preparations. The metabolic potency of thyroxine in equi-iodine amounts was, therefore, twofold to threefold that of the glandular products. The figures suggest that the iodine contained in the thyroxine molecule (acid insoluble) is perhaps a relatively more potent stimulating agent of metabolism than the iodine (partially acid soluble and partially acid insoluble) contained in the remaining gland. Plummer,[33] working with adults, arrived at similar conclusions. Confirmatory evidence is supplied by Kendall,[34] who noted that a portion of the iodine contained in the nonthyroxine fraction of the thyroid gland (acid soluble diiodotyrosine) was devoid of calorigenic activity. We wish to state, however, that the aforementioned interfering variables and the few subjects studied render the calculations regarding potency tentative and subject to modification. The results do suggest, nevertheless, that the iodine content affords the best single criterion of the calorigenic potency of thyroid extracts in human subjects. As previously mentioned, this relation between thyroid activity and iodine content has already been demonstrated by other methods of assay in animals.[32]

COMMENT

The present study of thyroid therapy in normal infants in conjunction with the available data in the literature brings to light several points of physiologic interest. The experimental evidence appears

32. Footnotes 4, 5, 6, 7 and 8. Metabolic studies on two human subjects by Dr. C. C. Sturgis are quoted by Hunt (footnote 4 *c*).

33. Personal communication from Plummer, quoted by Kendall (footnote 34).

34. Kendall, E. C., and Simonson, D. G.: Seasonal Variations in the Iodine and Thyroxine Content of the Thyroid Gland, J. Biol. Chem. **80**:357 (Dec.) 1928.

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adequate to establish two facts: first, in sufficient amounts, thyroid substance exerts a calorifacient action in subjects without hypothyroidism of all ages and often induces toxic symptoms charactertistic of hyperthyroidism, and second, the metabolic response of these subjects to smaller dosages of the drug is inconstant, but the minimum effective dosage always exceeds the therapeutic amounts effective in patients with hypothyroidism. These facts have led Plummer[35] to formulate the general rule, accepted by most workers in the field, that the stimulating effect of externally administered thyroid varies inversely with the intrinsic secretion in the organism. To explain the increased tolerance of subjects without hypothyroidism to thyroid medication, these authors have postulated a number of physiologic mechanisms which are in a measure supported by experimental evidence. In the first place, they assume a partial or complete cessation of intrinsic thyroid secretion coincident with the external administration of thyroid extracts.[36] This hypothesis receives support from anatomic studies of the thyroid glands of animals who had been treated during life with thyroid products.[37] The net result, therefore, would merely be a replacement of intrinsic by extraneous thyroid secretion without necessarily stepping up the total amount of thyroxine circulating in the body. It is notorious that small amounts of thyroid substance, even when parenterally administered, yield inconstant results in subjects without hypothyroidism, at all ages.[38] Only when this threshold of tolerance which varies markedly in different persons is exceeded by larger dosage, does the energy metabolism rise above the normal level and do clinical manifestations appear.

An additional safety factor which further increases the tolerance of normal subjects to thyroid therapy is postulated by a number of investigators.[39] This mechanism, which presumably begins to function at normal levels of metabolism, is assumed to be capable of dealing with the excess of thyroxine circulating in the body by accelerating elimination from and storage within the tissues. It has been shown that thyroxine may be stored directly in the normal thyroid gland under certain conditions,[35] when an excess is circulating in the blood.

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35. Footnote 18 *b*.

36. Footnotes 18 *a* and 24 *a*. Boothby, W. M., and Sandiford, I.: Quantitative Estimate of the Catalytic Power of Adrenalin and Thyroxin as Calorigenic Agents and the Relative Rates of Their Destruction, J. Biol. Chem. **59**:40, 1924. Plummer, W. A.: Clinical Features of Thyroid Disease, Ann. Clin. Med. **1**:259, 1923.

37. Footnote 1 *a*. Loeb, L.: Studies on Compensatory Hypertrophy of Thyroid Gland: Influence of Iodine on Hypertrophy of Thyroid Gland, J. M. Research **41**:481 (May) 1920.

38. Footnotes 2 *i* and 24 *a*.

39. Footnote 22 *a*.

Kendall [40] administered a single enormous dose of 200 mg. of thyroxine intravenously to a normal dog without inducing a greater rise in metabolism than that obtained with a much smaller amount. In the former instance, he found as much as 43 per cent of the total intake eliminated in the bile and 13 per cent in the urine fifty hours following the injection.

Regardless of the theoretical aspects of the problem, it seems certain that differences in metabolic response of normal persons and of those with hypothyroidism to thyroid substance are solely quantitative in nature, these differences probably arising from the presence, in the former instance, of intrinsic secretion and of a safety mechanism to deal with the excess of thyroxine circulating in the blood. The mass of available evidence is, in our opinion, as yet inadequate to support the view that the calorigenic response of the growing organism to thyroid therapy is unique or essentially different from the response evoked in the fully grown organism.[41] It is conceivable but not as yet established that the minimum effective dosage of thyroid capable of producing metabolic stimulation may fluctuate at the different age levels depending on constitutional and uncontrollable factors. However, when this threshold of dosage is exceeded, a calorifacient action is the inevitable result, irrespective of age.

Suggestive evidence has also been presented in this study of the correlation between thyroid potency and iodine content as tested by the metabolic response of normal infants. This evidence cannot be regarded as conclusive because of the individual susceptibility of our normal subjects to thyroid substance and because of the variable absorption of the drug from the gastro-intestinal tract following oral administration. Notwithstanding these limitations, it is noteworthy that the evidence of correlation obtained by metabolic methods in these normal infants closely parallels the reported result obtained in animals by other methods of assay. At the present time, the iodine content would seem to afford the best single criterion of the potency of thyroid extracts. It is recommended that only thyroid products of known iodine content be employed as therapeutic agents.[42]

SUMMARY AND CONCLUSIONS

The results of this study of the effect of thyroid therapy on the energy exchange of normal infants may briefly be summarized as follows:

40. Kendall, E. C.: The Physiologic Action of Thyroxin, Endocrinology **3**: 156, 1919.

41. Footnote 3, *b* and *c*.

42. Strauss, S. G.: Endocrine Gland Extracts, New York M. J. **113**:395 and 468, 1921.

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1. Thyroid extracts, in adequate dosage, exert a calorifacient action in infants with apparently normal thyroid glands and often induce in these subjects clinical symptoms characteristic of spontaneous hyperthyroidism.

2. The metabolic response of these subjects to thyroid extracts in smaller dosage is inconstant.

3. The minimal amounts of the drug capable of producing profound clinical and metabolic reactions in infants without hypothyroidism are apparently comparable to the dosage required to induce a similar response in adults without hypothyroidism. They notably exceed the usual dosage effective in subjects of all ages with hypothyroidism.

4. The usual persistence of thyroid action in these normal infants was approximately two to three weeks. This time interval coincides with the usual duration of thyroid action reported for normal adults and is considerably shorter than the persistence of such action in subjects with hypothyroidism.

5. In terms of absolute dosage, the whole gland product and the desiccated extract vary markedly in their potency as calorigenic agents, but they are equally potent when judged by their iodine content. On the latter basis, thyroxine, the active principle of the thyroid hormone, appears to be the most potent calorigenically of the three products.

6. A theoretic consideration of the constitutional factors which may explain the variable calorigenic response to thyroid therapy in subjects with and without hypothyroidism was presented in the text. Reference was also made to the clinical applications suggested by the physiologic and pharmacologic data.

HYMENOLEPIS NANA

REPORT OF ADDITIONAL CASES AND AN EXPERIMENTAL TRANSMISSION FROM MAN TO RATS *

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During the course of a survey on the intestinal protozoan infections among 362 children in St. Louis by one of us [1] (Dr. Tsuchiya), three cases of infection with Hymenolepis nana were incidentally encountered. Two of the patients came from an orphanage; the other, from a hospital. Though the infection is known to be common in crowded institutions, as exemplified by the report of Frey,[2] who found this infection present in 86 among 270 children (32 per cent) in an orphanage in Texas, the number of cases reported in the country at large has been low as compared with the studies made elsewhere. Goldman [3] has systematically reviewed most of the literature up to 1920. He reported, in addition, seven cases in a colored family, which were the first instances described in St. Louis. Spindler [4] recently reported that of 2,152 examinations of stools made during a survey in southern Virginia, 77 gave positive results for Hymenolepis nana, whereas Maplestone [5] observed thirteen cases among 72 children in an orphanage at Townsville, Queensland, and Hill and Sanchez [6] at Hatillo, Porto Rico, found 47 inmates with the infection in an orphanage for boys. Espie [7] found this infection present in

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1. Tsuchiya, H.: The Incidence of Protozoan Infections of Intestinal Tract Among Children in St. Louis, Proc. Soc. Exper. Biol. & Med. **28**:709, 1931.

2. Frey, J. H.: Helminthiasis at Texas State Orphans Home, Texas State J. Med. **11**:229, 1915.

3. Goldman, A.: Hymenolepis Nana; Possible Cercocystis Stage, Arch. Int. Med. **26**:373 (Sept.) 1920.

4. Spindler, L. A.: On the Occurrence of the Rat Tapeworm (Hymenolepis diminuta) and the Dwarf Tapeworm (Hymenolepis nana) in Man in Southwest Virginia, J. Parasitol. **16**:38, 1930.

5. Maplestone, P. A.: A Note on Hymenolepis nana in North Queensland, M. J. Australia **17**:394, 1920.

6. Hill, R. B., and Sanchez, A.: The Presence of Hymenolepis nana in Porto Rico, J. A. M. A. **83**:766 (Sept. 6) 1924.

7. Espie, A.: Sur l'existence de Hymenolepis nana en Tunisie, Arch. Inst. Pasteur de Tunis **14**:340, 1925.

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28 of 396 examinations of stools at one time, and later 30 cases among 600 persons from a civil prison in Sfax. Pons,[8] however, was able to find only eight cases of the infection in 2,500 examinations of stools in Cochin-China. The incidence of infection among the children examined by us might have been higher, if the methods specifically designed to detect helminth ova had been used in addition to those employed in the survey of intestinal protozoa.

There is considerable diversity of opinion as to the pathogenicity of this parasite. The consensus seems to indicate that if the parasite is present in large numbers, it may give rise to gastro-intestinal or generalized toxic symptoms that may lead to a chronic state. On the other hand, when few parasites are present, there may be no appreciable symptoms. Four of Goldman's patients [3] showed diarrheic symptoms and marked eosinophilia, while in the remaining three cases, there was no clinical evidence. Schloss [9] claimed that a marked eosinophilia was observed only in cases with a definite symptomatology, while infections without symptoms were not accompanied by eosinophilia. The symptoms described by Schloss were those of gastro-intestinal disturbances, abdominal pain, nausea and vomiting, as well as those of reflex nervous origin, such as restlessness and irritability. Examination of the blood made in three of his cases showed the characteristic picture of secondary anemia. Narr [10] reported eosinophilia in twenty-five cases, the highest being 16 per cent and the lowest, 4 per cent. The symptoms observed in these cases were chiefly convulsions, vomiting, diarrhea, abdominal pain and loss of appetite. Maplestone [5] found gastro-intestinal derangements with nervous symptoms, though once he observed abundant ova in the stool of an apparently healthy child of 10 years. Saeki [11] is inclined to believe that there exists a close relationship between the appearance of toxic symptoms and the number of ova in the stool. Espie,[7] on the other hand, found that none of the patients among natives of Sfax exhibited clinical symptoms, while a great majority of the infected Europeans suffered from gastro-intestinal disturbances, indicating the possibility of a racial immunity in the infection with Hymenolepis nana.

REPORT OF CASES

CASE 1.—Since he was able to talk, A. P., a boy, aged 9 years, had complained of abdominal pain or tenderness, usually at night, but, except for a summer diarrhea

8. Pons, R.: Existence d'Hymenolepis nana (von Siebold 1852) en Cochinchine, Bull. Soc. path. exot. **18**:722, 1925.

9. Schloss, O.: The Dwarf Tapeworm (Hymenolepis nana) as an Intestinal Parasite of Children with the Report of Fourteen Cases, Arch. Pediat. **27**:100, 1910.

10. Narr, F. C.: The Occurrence of Hymenolepis nana Infestation in an Institute for Children, Arch. Pediat. **36**:639, 1919.

11. Saeki, Y., quoted by Miyagawa, Y.: Clinical Parasitology, ed. 1, Tokyo, Kokuseido Publishing Company, 1927.

in early infancy, no diarrhea or blood in the stool had occurred. Other symptoms, such as anemia, headache, voracious appetite, nausea or vomiting, were not observed. The patient was a well nourished and well developed child, with good color. With the exception of moderately large tonsils and protruding abdomen, which, however, was not extreme enough to be abnormal at this age, physical findings were normal. Examination of the blood showed: hemoglobin, 80 per cent; red blood cells, 4,350,000; white blood cells, 7,200; differential count: polymorphonuclears, 51 per cent; eosinophils, 3.5 per cent; basophils, 0 per cent; transitionals, 4.5 per cent; small lymphocytes, 34 per cent; large lymphocytes, 7 per cent; Arneth index, 64.5 per cent. The benzidine test for occult blood in stool was positive, and there were a large number of ova of Hymenolepis nana, together with many cysts of Giardia lamblia and a few cysts of Endameba coli.

Case 2.—P. P., a girl, aged 6, the sister of the boy in case 1, with the exception of diarrhea at 6 months of age which did not progress to bloody stools, had no history of abdominal pain, nausea, vomiting, anemia, headache, dizziness or change in appetite. She was also well nourished and had good color. On examination, the abdomen was large, but there were no masses, ascites or gaseous distention. In this child, visceroptosis was present, owing to poor posture. With the exception of hypertrophic tonsils, the rest of the physical examination gave normal results. Examination of the blood showed: hemoglobin, 85 per cent; red blood cells, 5,360,000; white blood cells, 5,200; differential blood count: polymorphonuclears, 51.5 per cent; eosinophils, 2 per cent; basophils, 0 per cent; transitionals, 2 per cent; small lymphocytes, 36.5 per cent, and large lymphocytes, 8 per cent; Arneth index, 54.5 per cent. Examination of the stool showed no mucus or occult blood. There was a large number of ova of Hymenolepis nana with numerous cysts of Giardia lamblia and a few specimens of Enterobius vermicularis. Both of the children had always lived in large cities and had received good care.

Case 3.—Q. P., a boy, aged 11 years, was admitted to a hospital on account of osteomyelitis. Examination of the stool revealed many ova of Hymenolepis nana. Tests for occult blood in the stools were negative. This patient, however, was not available for further study at this time.

The patients in cases 1 and 2 were treated with oil of chenopodium in divided doses followed by a saline purgative. However, no worms were recovered by this treatment. The second treatment with oil of aspidium followed by magnesium sulphate, a method essentially similar to that advocated by Magath and Brown,[12] was given seven weeks later. The number of worms expelled by this treatment were very few. Examination of the stools made two months after the second treatment revealed a few ova of Hymenolepis nana in the stools of both children.

Though it is admitted that these cases were too few to justify the deduction of a reasonable conclusion regarding the pathogenicity of Hymenolepis nana, neither the laboratory nor the clinical pictures were indicative of a pathologic condition. In spite of the presence of large numbers of ova in the stools, diarrhea, anemia and abdominal pain were

12. Magath, T. B., and Brown, P. W.: Standard Method of Treating Tapeworm Infestation in Man to Recover the Head, J. A. M. A. **88**:1548 (May 14) 1927.

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absent in these cases. Furthermore, there was no evidence of nervous or nutritional disturbances; nor was there eosinophilia. Judging from these findings, we are inclined to believe that the two cases represent the type of hymenolepis infection in which a definite symptomatology is not observed.

CROSS-INFECTION BETWEEN MAN AND RAT

Grassi [13] expressed the view that the human and rat species of Hymenolepis were identical. His conclusion was based on the results obtained when one of six children to whom gravid segments of the rat species were fed was infected with the parasite. The majority of the subsequent workers were inclined to believe that these two species were physiologically distinct, though similar morphologically. Attempts to produce the infection by feeding rats with the ova of Hymenolepis nana terminated in failure. Goldman [3] fed eggs and matured segments to six rats and six mice, with negative results. Joyeux [14] and Chandler [15] similarly were not successful in the production of experimental hymenolepis infection in rats with materials from human beings. They suggested the view that the species of the parasite found in human beings has deviated from the ancestral habits and has lost its ability to develop in an intermediate host. Scott [16] likewise considered the two species distinct, and disposed of the possibility of cross-infection. Saeki,[17] however, by placing the problem on a careful experimental basis, was able to induce cross-infection between man and rats, and concluded that man might readily be infected by the ingestion of ova in food or drink contaminated by rats. Though he failed to detect any ova in his own stools after swallowing 1,000 eggs at one time, he was able to produce experimentally an infection in a 4 year old girl by feeding her a similar number of ova. Uchimura [18] likewise obtained a positive result, and reported that the ova of Hymenolepis nana and Hymenolepis murina hatched to develop into cysticercoids in the wall of the small intestine of albino rats without passing through an intermediate host. Since both species were similar morphologically, he concluded that they were the

13. Grassi, B.: Entwicklungscyclus der Taenia nana, Centralbl. f. Bakt. **1**:305, 1895.

14. Joyeux, C.: Hymenolepis nana et Hymenolepis fraterna, Ann. de parasitol. **3**:270, 1925.

15. Chandler, A. C.: Species of Hymenolepis as Human Parasites, J. A. M. A. **78**:636 (March 4) 1922.

16. Scott, H. H.: Stages in the Direct Development of Hymenolepis longior Baylis, J. Helminthol. **2**:173, 1924.

17. Saeki, Y.: Experimental Studies on the Development of Hymenolepis nana, Jikwa Zasshi, **238**:203, 1920.

18. Uchimura, R.: On the Development of Hymenolepis nana and Hymenolepis murina, Jikwa Zasshi, **240**:268, 1922.

same parasite. Woodland [19] confirmed the results of Saeki [17] and Uchimura,[18] and claimed that by feeding thirty of fifty-seven parasite-free rats with the ova of Hymenolepis nana, he was able to detect the infection in seven (23.3 per cent), and in later experiments in twenty-three out of twenty-seven rats, while the twenty-seven controls remained free from parasites.

That an intermediate host was not necessary in the transmission of hymenolepis infection was stated by Grassi.[13] He infected clean rats with gravid segments of rat parasite, and observed the successive stages of development in the animals until ova made their appearance in the stools on the thirteenth day. This result was later confirmed by Joyeux,[14] Saeki [17] and Woodland.[19]

Ova of H. nana from the stools of the subjects in cases 1 and 2 were carefully collected by the method of Hegner [20] for obtaining washed cysts of intestinal protozoa. Stool containing ova was thoroughly emulsified in a large quantity of water. This was first filtered through a sieve to remove coarse débris, and then through three layers of gauze. The emulsion was poured into a tall cylinder and allowed to stand for a few hours. The supernatant fluid was decanted, and the sediment again stirred up in water. The ova were again allowed to settle to the bottom, and this process was repeated at least three times until the sediment was found to be composed of the ova and a small amount of débris. The superiority of this method to those generally used in the studies of helminth ova was obvious, as by this treatment the least structural disturbance was observed in the ova which were subsequently fed to rats. The ova of H. nana are known to be comparatively nonresistant to environmental conditions. Injury due to a brine-floatation or a concentration method may cause the ova to disrupt, thus rendering their oncospheres incapable of penetrating the intestinal villi where they develop later into cysticercoids.

Prior to the feeding of rats with washed ova thus prepared, six rats 7 weeks of age were carefully examined for the presence of H. nana. Fresh fecal pellets from these rats were obtained for ten consecutive days, during which time three doses of magnesium sulphate were given in an effort to expel ova if any were present. These rats were found to be free from hymenolepis infection. In two of them, however, Trichomonas muris was found, and in one, cysts of Giardia muris, while the remainder were apparently parasite-free. These rats were fed on a milk and bread diet during the entire period of the experiment. Each of them was fed 1 cc. of washed ova, and daily examination of fecal

19. Woodland, W. N. F.: Hymenolepis nana and Hymenolepis fraterna, Lancet **1**:922, 1924.

20. Hegner, Robert: Excystation and Infection in the Rat with Giardia lamblia from Man, Am. J. Hyg. **7**:433, 1927.

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pellets were made to eliminate the least possibility of infection prior to the experiment. In one of three rats fed on washed ova from the patients in case 1, a few ova of H. nana appeared in fecal pellets on the forty-second day, while in one of three rats receiving the washed ova from the patient in case 2, ova appeared on the forty-fourth day. In the remaining four rats the infection apparently did not develop, as the fecal pellets examined during sixty-eight days following the feeding revealed no ova of H. nana. This may be accounted for by differences in individual susceptibility.

On the two rats in which the infection had developed, autopsy was performed two weeks after the initial appearance of ova. On examination of the lower part of the ileum, there were found six adult worms in one rat and ten in the other. None were found at the levels higher than 6 inches (15.24 cm.) proximal to the ileocecal valve. The worms ranged from 15 to 36 mm. in length and from 0.5 to 0.8 mm. in breadth.

Ova obtained from these two rats were subsequently used to infect two groups of five animals each of parasite-free young rats, 7 weeks old. According to the method previously described, ova were washed and prepared for oral administration. The infection developed in three of the five rats in the first group following feeding with the ova originally obtained from the subject in case 1, the incubation period being twenty-three, twenty-six and twenty-seven days. In the second group, the infection developed in two animals fed with the ova of the second rat originally infected by the ova of the second subject. The periods of incubation were twenty-five and twenty-six days, respectively. In no instance did ova appear on the thirteenth day as reported by Grassi,[13] Saeki [17] and others. Faust [21] suggested that even if cross-infection were possible between man and rats, the parasites would not develop as readily in rats as they do in man, in whose intestine the worms were originally developed. The incubation period in the experiments on cross-infections was considerably longer than that required in rat to rat infection. It is natural to assume that parasites that had developed in the human intestine should first be acclimatized to the intestinal conditions of rats before they are able to continue the life cycle.

The present study illustrates the possibility of cross-infection with H. nana from man to rats. There may be also the possibility of cross-infections among various hosts, such as domestic animals and birds, which may become the sources of infection. According to Sandground,[22] the closer the genetic relationship between two hosts, the more similar

21. Faust, E. C.: Human Helminthology, ed. 1, Philadelphia, Lea & Febiger, 1929.

22. Sandground, J. H.: Consideration of Relation of Host-Specificity of Helminths and Other Metazoan Parasites to Phenomena of Age Resistance and Acquired Immunity, Parasitology **21**:227, 1929.

will be the conditions, and hence less difficulty will be encountered in an attempt to bring about cross-infection between these hosts. Furthermore, recent work of Ackert and his associates [23] showed that resistance of young chickens to Ascaris lineata became noticeably lower when a diet deficient in vitamin A was fed to them for a period of five weeks. We may assume, therefore, that by modifying the diet in such a way as to lower the nutritional state of an individual, conditions that render the animal readily susceptible to invasion with a foreign parasite may be experimentally induced, whereas under normal conditions such an invasion may not be possible.

COMMENT

The factors underlying the mechanism of a successful cross-infection between man and rats depend on the susceptibility of the host and the aggressivity of the parasite. Though the age of the host was not the deciding factor in determining the susceptibility to infection with H. nana, it has previously been suggested by some that apparent changes in the tissues of the adult would render older persons less susceptible to the parasitic invasion. For this reason, the selection of younger animals is of prime importance in experimental study.

It is generally known that there exist specific relationships between host and parasite. Indeed, the selection of the host by the parasite can be regarded as an important step in the cross-infection. From the standpoint of the parasite, it has to seek a host that is less resistant and yet provides optimum environmental conditions on which it is successfully able to maintain its life cycle. Since the infection of the human species with Hymenolepis was successful in two of six attempts, an inference may be drawn with respect to the feasibility of the reverse condition; that is, that in certain cases the infection from rat to man is possible, as illustrated by the results of Saeki [17] and Uchimura.[18]

Sanitation and hygiene of crowded institutions, such as orphanages, present important problems in dealing with the transmission of hymenolepis infection. It was found that a common wash basin was being used by the inmates of the orphanage in question. Furthermore, rats were present in the storerooms.

SUMMARY

1. Two cases of hymenolepis infection (Hymenolepis nana) in St. Louis, in addition to those previously reported by Goldman,[3] are described. Neither clinical nor laboratory findings, however, were indicative of pathologic conditions in these children.

23. Ackert, J. E.; McIlvaine, M. F., and Crawford, N. Z.: Resistance of Chickens to Parasitism Affected by Vitamin A, Am. J. Hyg. **13**:320, 1931.

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2. With a view to determining the possible source of hymenolepis infection, a cross-infection experiment with ova from human sources was carried out in rats. The results of this study showed that two of six clean rats were successfully infected with H. nana. Subsequent experiments showed that five of ten clean rats were found to be infected with the ova of the two rats previously infected with human materials.

3. Since there is the possibility of acclimatizing human parasites in rats, rats in turn may become one of the sources of the infection in human beings.

INFLUENZAL MENINGITIS TREATED WITH SPECIFIC ANTISERUM AND COMPLEMENT

REPORT OF FIVE CASES *

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Influenzal meningitis [1] is an acute inflammation of the meninges caused by the influenza bacillus, accompanied often but not always by a bacteremia. In its clinical picture it cannot be distinguished from acute meningitis caused by other organisms, such as the meningococcus, pneumococcus and streptococcus. The relative success of specific serum treatment in meningococcus meningitis and the absence in the literature of any reported success with similar treatment in influenzal meningitis have stimulated this study.

In the course of this work, we gained the impression that the influenza bacillus was a more common cause of meningitis in young children than was generally supposed. This impression prompted a study of the relative frequency of this form of meningitis in children under 2 years of age, and we were surprised at the high percentage of cases that the records disclosed. The records of the Infant's and Children's Hospital for the last five years have been examined, and in that period 184 children under 2 years of age were admitted to the hospital with meningitis. Table 1 shows the relative frequency of the various infectious agents.

During the period under review, there was no epidemic increase of any particular type, so that table 1 represents the sporadic incidence of the various forms. It will be noted that there were 25 cases of influenzal meningitis compared to 56 cases of meningococcus meningitis. Of the 124 cases of acute purulent meningitis, the influenzal group accounted for no less than 20 per cent.

Spontaneous recoveries from this disease have been reported in the literature, but it is well known that the mortality is exceedingly

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1. The terms in common usage, "influenzal meningitis" and "influenza bacillus," are employed here instead of the more correct, but more awkward terms, "Pfeiffer bacillus meningitis" and "Pfeiffer bacillus." There is, of course, no assumption implied that there is any connection between this disease and epidemic influenza.

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high. Rivers [2] collected the largest number of cases, and he found a mortality of 92 per cent in a series of 220 cases, and in children under 2 years of age, the mortality was 97 per cent. In our group of cases, whether or not the children were treated specifically, the mortality was 100 per cent.

Rivers [2] drew attention to the fact that this is primarily a disease of infancy, 79 per cent of his cases being in children under 2 years of age. This has been our experience, and we have never seen a case in a child over 6 years of age. In the literature, a few cases in adults have been reported.

Attempts to treat patients with influenzal meningitis have met with no success, whether nonspecific methods, such as drainage and antiseptics have been used, or specific treatment by injecting antiserum

TABLE 1.—*Relative Frequency of Various Infectious Agents*

Organism Causing Meningitis	Number of Cases	Percentage of Total
B. tuberculosis	60	32.6
Meningococcus	56	30.4
B. influenzae	25	13.5
Pneumococcus	23	12.5
Streptococcus	14	7.5
B. acidi-lactici	1	0.5
Staphylococcus	1	0.5
B. coli-communis	1	0.5
B. lactis-aerogenes	1	0.5
Mixed infections	2	1.1

locally has been tried. Wollstein,[3] in 1911, was the first to use a specific antiserum, and she was able to treat successfully a Rhesus monkey with antiserum, twenty-four hours after infection. We can find no record of the use of this serum in human infections. Our attempts go back several years. Parker [4] had shown that the influenza bacillus secretes a toxic substance that can be demonstrated in the filtrates of young broth cultures, and that an antiserum can be prepared that contains neutralizing antibodies for this toxic substance. Accordingly, a horse was immunized with the toxic filtrates and also with dead and living bacilli. The serum from this horse was injected by the lumbar route into several patients with influenzal meningitis, but it did not influence the course of the disease.

2. Rivers, T. M.: Influenzal Meningitis, Am. J. Dis. Child. **24**:102 (Aug.) 1922.

3. Wollstein, M.: Serum Treatment of Influenzal Meningitis, J. Exper. Med. **14**:73, 1911.

4. Parker, J. T.: A Filtrable Poison Produced by B. Influenza (Pfeiffer), J. A. M. A. **72**:476 (Feb. 15) 1919.

Since this horse had been immunized mainly with pharyngeal strains of the influenza bacillus, another horse was given injections of formaldehyde-killed cultures of meningeal strains; Rivers [5] showed—and this has been our experience—that the meningeal strains fall into a group that is much more homogeneous serologically than the strains found in the pharynx or in other pathologic conditions. This serum was used in several cases, but still with no apparent influence, cultures of the cerebrospinal fluid being invariably positive throughout the course of the disease.

At this stage it became possible, largely owing to the establishment of the Philip Ellis Stevens, Jr., Memorial Fund for the study of this disease, to investigate the problem more thoroughly. In particular, attention was turned to the mechanism of the bactericidal action of the serum. Although the cerebrospinal fluid in these cases generally has a high cell count, it was found in test tube experiments that even with an efficient antiserum, the leukocytes can kill only very few influenza bacilli. Whereas if fresh normal serum, as well as antiserum, is present, large numbers of organisms are killed even in the absence of leukocytes. This, of course, is characteristic of gram-negative organisms, as opposed to the gram-positive organisms, in which phagocytosis is the main bactericidal mechanism. The cerebrospinal fluid from several cases was then studied for the presence of complement, the active constituent of fresh normal serum, and it was found to be completely absent in all cases, in contradistinction to cases of meningococcal meningitis, in which it has been present in all cases so far investigated. The absence of complement in these cases has been pointed out previously by Kolmer.[6] The injection of either fresh human serum or fresh guinea-pig serum was thus clearly indicated, as has been advocated by Kolmer.[6]

The efficiency of the antiserum was investigated at the same time. Unfortunately, this disease cannot be reproduced in its human form in the ordinary laboratory animal, so that one is forced to fall back on in vitro experiments to test the antiserum. It is customary in these circumstances to rely on the agglutination test as a measure of the potency of the antiserum. The antiserum that we had used up to this point agglutinated the organisms isolated from the cases up to a fair titer. However, when this antiserum (*A*) was used in the presence of fresh serum in a bactericidal test, it was found to have very little action, although it agglutinated the organism used in the test up to a dilution of 1:1,000. This antiserum was the product of two months' immunization. We then tested a specimen of antiserum (*B*) from the

5. Rivers, T. M., and Kohn, L. A.: The Biological and the Serological Reactions of Influenza Bacilli Producing Meningitis, J. Exper. Med. **34**:477, 1921.

6. Kolmer, J. A.: The Mechanism of Immunological Changes in the Cerebrospinal Fluid, Proc. A. Research Nerv. & Ment. Dis. **4**:71, 1924.

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same horse after twelve months' immunization. The agglutination titer had only risen to 1:8,000, but, as will be seen from table 2, it now had a very strong bactericidal effect. The bactericidal test was carried out by a technic described by one of us (Dr. Ward [7]) when working with the pneumococcus and adapted in these experiments to the influenza bacillus. It consists in incubating (for twenty hours in a rotating machine) varying numbers of the organisms in closed tubes containing mixtures of fresh normal blood and antiserum. The amount of normal blood is kept constant, and by titrating both the antiserum and the organisms, it is possible to determine the least amount of antiserum that shows definite bactericidal power. The details of the method will be found in the original paper,[7] the only modifications introduced being the substitution of fresh normal rabbit blood diluted with equal parts of saline solution for human blood and the addition to each tube of

TABLE 2.—*Effect of Antiserum in Different Dilutions*

Number of Influenza Bacilli Added to Tube	Concentration of Antiserum*										
	Antiserum A (Agglutinates 1:1,000)					Antiserum B (Agglutinates 1:8,000)					
	1:25	1:250	1:2,500	1:25,000	1:250,000	1:25	1:250	1:2,500	1:25,000	1:250,000	Saline
200,000	+	+	+	+	+	+	+	+	+	+	+
20,000	+	+	+	+	+	+	0	0	+	+	+
2,000	0	+	+	+	+	+	0	0	+	+	+
200	0	+	+	+	+	+	0	0	0	+	+
20	0	0	0	0	0	+	0	0	0	0	0

* + indicates growth; 0, sterility.

0.15 cc. of 5 per cent pepsin-digested blood broth [8] in order to supply sufficient growth factors for the influenza bacillus. The method gives consistent and clearcut results. The influenza bacillus used in this experiment was freshly isolated from a case, and had all the characteristics of a "smooth" virulent organism. It was grown in Fildes' [8] pepsin-digested blood broth for eighteen hours.

Table 2 shows that antiserum *B* has a slight action even in a concentration of 1:25,000 (compare with saline control), whereas antiserum *A* acts only in a dilution of 1:25. The strong antiserum *B* shows very clearly the Neisser-Wechsberg phenomenon in that a concentration of 1:25 has no action, while a concentration of 1:250 or 1:2,500 has the maximum effect. In other words, one may have too much as well as too little antiserum for effective bactericidal action. Whether or not the Neisser-Wechsberg phenomenon is an actual factor in the treatment in these cases has still to be determined. It is possible that we

7. Ward, H. K.: Observations on the Phagocytosis of the Pneumococcus by Human Whole Blood, J. Exper. Med. **51**:675, 1930.

8. Fildes, P.: A New Medium for Growth of B. Influenzae, Brit. J. Exper. Path. **1**:129, 1920.

are giving too much antiserum for the concentration of complement present, when the injected fresh serum has been diluted by the spinal fluid. The reasons underlying the very different bactericidal effect of these two antiserums, which differ so little in their agglutination titer, will be presented in another paper.

The last four patients with influenzal meningitis whom we have had at the Infant's and Children's Hospital have been treated with fresh human serum and the efficient antiserum *B*. In addition, we have the complete record of a patient who was treated with the same materials in Bellevue Hospital, New York, This patient was on Dr. C. H. Smith's service.

To sum up the effects of this treatment in these cases, it is obvious that we cannot claim to have solved the problem of the specific therapy for influenzal meningitis, since all five children died. However, they all present the encouraging feature that at one time or another, in three cases for some days, the cerebrospinal fluid was sterile and nearly normal in other respects. Only two autopsies were obtained, but from a study of these and from observations during life in another case, it appears that abscess cavities are walled off somewhere in the subarachnoid space, and so far, specific or surgical treatment has been powerless to deal with these pockets effectively. It is apparently not very difficult to sterilize the free cerebrospinal fluid—this applies to the ventricular as well as the lumbar fluid—but a method has yet to be devised, either surgical or specific, or both, to treat the walled-off abscesses, which presumably in the end overwhelm the patient.

TREATMENT

The details of the treatment at present employed are as follows:

Fresh serum for complement is obtained daily by withdrawing from 30 to 40 cc. of blood from an adult, allowing it to clot and, after centrifugation, aspirating off the serum, which is then ready for administration with the anti-influenzal serum. At each treatment from 6 to 8 cc. of normal serum plus 15 cc. of influenza serum is injected. These treatments are given twice a day, one injection into the lumbar subarachnoid space, the other into one of the ventricles. This alternation is maintained throughout the course. In younger infants with an open anterior fontanel, the needle is inserted through the lateral margin of the fontanel and pushed directly into the anterior horn of the lateral ventricle. In older infants with a closed anterior fontanel, bilateral trephine openings are made in the occipitoparietal regions just lateral to the midline, and injections are made into the posterior horns of the lateral ventricles. Occasionally, cisternal injection has been used. At each treatment as much cerebrospinal fluid as possible is withdrawn.

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Usually from 3 to 50 cc. is obtained. In each instance the amount of serum-complement mixture injected is governed by the amount of fluid withdrawn.

When a positive blood culture was present, 50 cc. of antiserum was given intravenously. We have found positive blood cultures to be relatively frequent. Transfusion has been given occasionally when indicated in the individual patient.

Further surgical treatment other than the simple trephines for ventricular injection will be described in the summary of the individual cases.

REPORT OF CASES

The individual case records of patients treated with fresh serum and the efficient antiserum have been summarized briefly.

CASE 1.—S. M., a boy, aged 6 years, was admitted to the hospital on Dec. 16, 1930, with a history and physical findings consistent with acute meningitis of eighteen hours' duration. Lumbar puncture showed a cloudy fluid in which influenza bacilli were demonstrated by direct smear and culture. For four days he was treated with complement and inefficient antiserum *A*. No diminution in the number of organisms was noted during this period. On the fifth day, an efficient antiserum was used with the complement, and the organisms began to diminish until on the seventh day the spinal fluid was sterile. Treatment was stopped at this point. The next day the fluid again showed organisms, and treatment was begun again. From this point further specific treatment had no effect on the organism, which increased in number until the time of death, the fluid becoming more cloudy. At autopsy, the meninges showed less diffuse inflammation than is usually present in these cases. There were, however, a number of scattered, walled-off foci, particularly about the base. There were a few similar areas in some of the sulci over the cortex.

CASE 2.—J. M., a boy, aged 21 months, was admitted to the hospital on Jan. 27, 1931, showing symptoms and physical signs of acute meningitis of two and one-half days' duration. Lumbar puncture revealed a cloudy fluid in which influenza bacilli were demonstrated by direct smear and culture. During the first two days the patient was treated with complement and serum by the lumbar route. On the third day, bilateral trephine openings were made, and thereafter treatments were alternated between the lumbar and ventricular routes. On the first day, he was given 20 cc. of serum intravenously, and again on the eighth day 60 cc. of serum was given intravenously. There was a gradual diminution in the number of organisms in the spinal fluid, until two days before death, when the spinal fluid was sterile for four successive taps. The last tap just before death was again positive. The patient died on the twelfth day after admission. Autopsy was not obtained, but the clinical picture during the last two or three days was that of a marked basal meningitis. The fact that the cerebrospinal fluid during this period was sterile and relatively clear, together with a continued high temperature, suggests that the patient died from walled-off inflammation, particularly about the base, rather than from a generalized infection in the subarachnoid space.

CASE 3.—G. B., aged 21 months, was admitted to the Bellevue Hospital on Dec. 30, 1930, on the service of Dr. Charles H. Smith. The patient had had

symptoms of acute meningitis for five days before admission, and specific treatment (with serum sent by us) was started on the sixth day after admission. The patient received seven injections of antiserum plus complement during the next five days. After the first day of treatment the spinal fluid became sterile and continued sterile for eight days. During this period the child showed marked clinical improvement, the temperature was lower, and the spinal fluid cell count fell to 10 per cubic millimeter. Three days after the treatment was discontinued the patient had a relapse, and the spinal fluid again showed influenza bacilli. The cell count rose, and in spite of resumption of specific serum treatment, the patient showed no improvement and died four days later with Streptococcus hemolyticus in the blood stream and spinal fluid. No autopsy was obtained.

CASE 4.—M. A., a girl, aged 16 months, was admitted to the hospital for study because of an unexplained fever of five weeks' duration. Lumbar puncture was done to determine whether or not a chronic meningitis might be present, and a cloudy fluid was obtained which showed influenza bacilli by direct smear and culture. During the first four days she received two intraspinal injections of antiserum and complement daily. During this time there was a marked diminution in the number of organisms in the spinal fluid, and the patient showed some clinical improvement. On the fourth day, she was given 60 cc. of antiserum intravenously. Twelve hours later the patient showed a tendency to uncontrollable bleeding at lumbar puncture, and treatment had to be suspended on this account for six days. Blood studies indicated that the patient had suddenly acquired a secondary thrombocytopenic purpura, and for this reason she was given transfusions on two occasions, which resulted in prompt improvement in the purpura. Six days after suspension of intraspinal treatment, lumbar puncture showed an increased number of organisms. Specific treatment was resumed. Four days later the spinal fluid became sterile and remained so for the next eight days, during which time, however, two treatments daily were continued. At this point treatment was discontinued because the patient was apparently cured. There were no physical signs of meningitis, the temperature was essentially normal, and the spinal fluid had been clear and sterile for a long period. Six days later, because of a sharp rise in temperature, lumbar puncture was repeated, and the spinal fluid was again found positive. The next day bilateral trephine openings were made through which serum and complement were distributed over the cortex through a small catheter. Thereafter, alternate treatments were given into the ventricles and lumbar subarachnoid space. The patient died seven and one-half days later, having shown no clinical improvement and the spinal fluid continuing positive. Her terminal clinical picture was the same as in case 2. No autopsy was obtained.

CASE 5.—J. F., a boy, aged 9 months, was admitted to the hospital on April 29, 1931, with a history and physical signs of acute meningitis. Two weeks before admission the child had had an infection of the upper respiratory tract. One week before admission there was a change in symptoms pointing to the onset of meningitis at this time. Lumbar puncture yielded a cloudy fluid in which influenza bacilli were demonstrated by direct smear and culture. On the following day, bilateral trephine openings were made in the parieto-occipital region, at which time serum and complement were introduced over the cortex through a catheter. In the right trephine opening a small collection of thick pus was encountered. Throughout the entire course antiserum and complement were injected alternately into the ventricles and lumbar space.

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During the next five days, the organisms diminished greatly, and on the fifth day the spinal fluid became sterile and remained so for the next fourteen days. During the first five days, the temperature remained high, and there was no change in the patient's condition.

On the fifth day, bilateral subtemporal trephine openings were made and antiserum and complement introduced about the base of the brain. On the right side, a large amount of purulent fluid was encountered. On the left, the fluid was clear. For the next week there was striking clinical improvement in the patient, and then he gradually began to go downhill.

Ten days after the last operation, the right subtemporal trephine was reopened, and about 12 cc. of thick pus was aspirated. The area was washed out with antiserum and complement. Four days later this was again opened, and a drain was left in the abscess region. The patient did not improve, and died twenty-four days after admission. The cerebrospinal fluid became positive again two days before death. On admission, the blood culture was positive and became sterile after treatment with antiserum. Two days before death it was again positive.

At autopsy two extensive abscess areas were found, one involving about half the area of the right cerebral cortex, and the other involving the base. The rest of the surface of the cerebrum and cerebellum was congested, but there was no exudate, and the demarcation of the boundaries of the abscess areas was very sharp and distinct. It was evident that these abscess areas were effectively shut off from the rest of the subarachnoid space.

COMMENT

Acute meningitis caused by the influenza bacillus differs from meningococcus meningitis in several respects, and these differences may explain why specific treatment has been unsuccessful so far in curing the former disease. In the first place, the influenza bacilli are present in enormous numbers in the cerebrospinal fluid, whereas in meningococcus meningitis the organisms are generally few. In the second place, complement is absent in the influenzal type, but in all the cases of meningococcus meningitis we have investigated, it has been present. Phagocytic cells are present in the cerebrospinal fluid in both diseases, but test tube experiments show that the bactericidal action of complement and antiserum is incomparably stronger than the action of white cells and antiserum. The explanation of this difference in complement content in the two diseases still has to be sought.

Lastly, in the two autopsies that we performed in these five cases, abscesses definitely walled off from the rest of the meninges were demonstrated. This is evidently more characteristic of influenzal meningitis than of meningococcal meningitis. It is this difference between the two diseases that is the most important from a therapeutic point of view, because the wall of the abscess places a mechanical obstruction in the path of an otherwise successful serum treatment for influenzal meningitis. For it is clear from these five cases that it is possible to sterilize the general subarachnoid space by injecting fresh normal serum and an efficient antiserum, and the problem turns on those areas that are

evidently shut off fairly early in the disease. As always, prevention is better than cure, and in those cases that come under treatment early, it may be possible, by using the optimum concentrations of complement and antiserum, to sterilize the subarachnoid space more rapidly, in this way perhaps preventing the formation of pockets, which we cannot reach by simple injection later in the disease. The surgical treatment of these pockets, once they are formed, is obviously far from an easy problem, because of their extent and the difficulty in localizing them.

CONCLUSIONS

1. Five patients with acute meningitis caused by the influenza bacillus have been treated locally by the injection of fresh normal serum and an efficient specific antiserum.

2. All of the patients died eventually, but in every case the cerebrospinal fluid was sterilized for varying periods, up to fourteen days.

3. The cause of death was almost certainly due to a localization of the inflammatory process in areas that were shut off from the general subarachnoid space, and so protected from the action of the complement and the specific antiserum.

The Massachusetts Antitoxin Laboratory took the trouble to immunize horses for us. Mr. A. P. Batchelder and Dr. J. Wright gave us much laboratory assistance. Dr. F. D. Ingraham cooperated in the surgical treatment.

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CHANGES OF THE BLOOD LIPID IN CHILDREN

FOLLOWING THE APPLICATION OF ANHYDROUS WOOL FAT AND ULTRAVIOLET IRRADIATION *

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In a preliminary report [1] on the changes in the blood cholesterol of children, it was shown that the cholesterol content of the blood might be increased by the combined use of inunctions of wool fat and ultraviolet irradiation. The patients in the cases then reported were treated for a period of only sixteen days. In the present report, a study of thirty-two additional cases in which intensive treatment was given is recorded.

PROCEDURE

Ultraviolet rays were applied with a Hanovia quartz mercury lamp at a distance of 30 inches (76 cm.), exposures being given anteriorly and posteriorly, three times weekly. The time of exposure was three minutes at first and then was increased to five, seven, ten, twelve and fifteen minutes, respectively, on subsequent exposures. Wool fat, U. S. P.,[2] softened by heat, was rubbed well into the entire body; the patient then received the ultraviolet irradiation.

Technical Methods.—The cholesterol was determined by the method of Bernhard,[3] and Bernhard and Drekter;[4] free cholesterol, with Mueller's[5] modification of the Windhaus[6] gravimetric method, all weighings being made with the Bunge microbalance. For lipoid phosphorus, the digestion method proposed by Bloor[7] and the colorimetric method of Benedict and Theis[8] were utilized.

The total alcohol ether extract, which includes all fats and lipoids extracted by alcohol ether, was determined as follows: A strip of fat-free filter paper was

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* From the Achelis Laboratory, and the A. Jacobi Division for Children, Lenox Hill Hospital.

1. Leopold, J. S., and Bernhard, A.: Arch. Pediat. **46**:756, 1929.
2. Anhydrous wool fat, U. S. P. was used.
3. Bernhard, A.: J. Biol. Chem. **35**:15, 1918.
4. Bernhard, A., and Drekter, I. J.: J. Lab. & Clin. Med. **16**:1225, 1931.
5. Mueller, J. H.: J. Biol. Chem. **25**:549, 1916.
6. Windhaus, A.: Ztschr. f. phys. Chem. **65**:110, 1910.
7. Bloor, W. R.: J. Biol. Chem. **36**:33, 1918.
8. Benedict, S. R., and Theis, R. C.: J. Biol. Chem. **61**:63, 1924.

cut in half lengthwise (about 160 mm.); then it was impregnated with 1 cc. of blood serum and spread out in such a manner that it occupied about seven eighths of the length of the paper. After drying in air for one-half hour, it was folded in a manner similar to a folded filter and placed in a Folin sugar tube, to which was added 4 cc. of a mixture of equal parts of 95 per cent ethyl alcohol and pure ethyl ether. A condenser[9] was placed in the Folin tube, and the mixture, on a slow boiling water bath, allowed the reflux for one hour. During the extraction, care must be exercised that the alcohol ether mixture does not evaporate below 3 cc. After the extraction was complete, the condenser was removed and the extract transferred to a weighed porcelain crucible; the tube was washed with four 5 cc. portions of the alcohol ether mixture, and the washings were added to the crucible. The extract, with the added washings, was evaporated on the water bath; the crucible was then placed in a desiccator for two hours, and weighed on the Bunge microbalance. All determinations were made in duplicate.[10] The same amount of alcohol ether was used in each tube. The results per hundred cubic centimeters of serum were: 1,120 mg. for 1 cc.; 2,250 mg. for 2 cc. and 3,350 mg. for 3 cc. The proportional recovery shows the comparative accuracy of the method. The error of the method is within 5 per cent.

The cholesterol esters were obtained by subtracting the free from the total cholesterol. The patients studied were grouped as follows: group A, those treated only by ultraviolet irradiation; group B, those treated with inunctions of nonirradiated and irradiated wool fat; group C, those treated with inunctions of wool fat and ultraviolet irradiation.

RESULTS

Values Found in Normal Children.—Specimens of the blood serum of thirty-five normal children between the ages of 3 and 12 years were examined in order to establish normal figures with our technical procedures. The high, low and average figures for this normal group are given in the accompanying table. All specimens of blood were obtained from patients in the fasting state.

Table Showing Lipids in the Blood of Normal Children

	Total Cholesterol, Mg. per 100 Cc.	Free Cholesterol, Mg. per 100 Cc.	Cholesterol Esters, Mg. per 100 Cc.	Total Alcohol Ether Extract, Mg. per 100 Cc.	Lipoid Phosphorus, Mg. per 100 Cc.
High	283	136	147	1,500	6.4
Low	143	64	79	980	4.2
Average	173	79	94	1,174	5.0

Values in Group A.—Eight patients were treated with ultraviolet irradiation only. In six of them, the figures for cholesterol showed practically no change. In two cases there was a rather marked increase

9. The apparatus is described in the paper on cholesterol by Bernhard and Drekter (footnote 4).

10. As a check on the efficiency of the extraction by alcohol ether, three sets of determinations were made on a serum, 1, 2 and 3 cc. being used for extraction.

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in the cholesterol after treatment with the rays alone. In the first case (no. 68,875), an initial blood serum cholesterol of 95 mg. and a total alcohol ether extract of 710 mg. were found. After twenty treatments with the rays, the cholesterol rose 92 mg., and the alcohol ether extract, 230 mg. No further significant rise occurred in any of the lipid fractions of the blood after fourteen additional treatments. During treatment, there was also a rise in free cholesterol of 30 mg. and a corresponding rise in cholesterol esters of 55 mg., while the lipoid phosphorus increased 3.7 mg.

The second case (no 63,676) showed a similar increase of the lipids. The initial cholesterol value was 75 mg., the alcohol ether extract, 540 mg., and the lipoid phosphorus, 4 mg. After thirty treatments with the ultraviolet rays there was an elevation of the blood cholesterol of 75 mg. and of the alcohol-ether extract of 480 mg., while the lipoid phosphorus remained unchanged. The lipoid phosphorus stability in this case is in contrast to the instability in the case previously mentioned.

Values in Group B.—Three patients received inunctions of non-irradiated wool fat for five consecutive days. In case 24,790, the initial cholesterol value was 66 mg., the alcohol ether extract, 580 mg., and the lipoid phosphorus, 2.4 mg. At the end of the five-day period, there was no change in the cholesterol content, but the alcohol ether extract increased 250 mg., and the lipoid phosphorus rose to 3.2 mg. There was a slight increase of 6 mg. in the amount of free cholesterol, and a fall of 8 mg. in the cholesterol esters. This patient was then given inunctions of wool fat that had been irradiated by ultraviolet rays for a period of one hour at a distance of 12 inches (30 cm.) After the fifth inunction, the blood serum cholesterol was increased 111 mg. and the cholesterol esters showed an increase of 61 mg., while the increase in free cholesterol was 52 mg. and the total alcohol ether extract increased 460 mg. There was only a slight rise in lipoid phosphorus. After the tenth and fifteenth inunctions, the figures for the lipid partition remained approximately the same. The significant increase in the lipids, especially the sterols, as compared to the period before treatment may be definitely attributed to the effect of the irradiation of the wool fat by ultraviolet rays.

Bernhard and Drekter [11] have shown that after ultraviolet irradiation of wool fat, there is a marked rise in the amount of sterols that can be precipitated by digitonin. In case 21,918, the second of this group, there was an initial cholesterol value of 100 mg. and a total alcohol ether extract of 630 mg. After five inunctions of nonirradiated wool fat, the only change was in the total alcohol ether extract, which increased 295 mg. All other lipid fractions remained practically

11. Bernhard, A., and Drekter, I. J.: J. Biol. Chem. **93**:1, 1931.

unchanged. Eleven inunctions of irradiated wool fat were then given, after which there was a rise in cholesterol of 88 mg. The increases in the other lipid fractions were as follows: free cholesterol, 32 mg.; cholesterol esters, 46 mg., and total alcohol ether extract, 770 mg.; changes in the lipoid phosphorus were unimportant.

In the third case (no. 4,987), the patient reacted in a manner similar to that of the patients just cited. The initial cholesterol was 70 mg., and the total alcohol ether extract, 796 mg. No examinations of the blood were made after the fifth treatment with plain wool fat. After the tenth treatment with irradiated wool fat, the increases in lipids were as follows: cholesterol, 30 mg., alcohol ether extract, 304 mg., free cholesterol, 24 mg., and the cholesterol esters, 6 mg. Lipoid phosphorus remained unchanged. One year later, the lipid fractions had remained unchanged, with the exception of the cholesterol esters, which had risen 14 mg.

Values in Group C.—This group consisted of twenty-seven patients, who had received inunctions of wool fat followed by ultraviolet irradiation. Six patients (group 1) were used as controls; they received only ultraviolet irradiation for a period; they were then given a rest, and finally they were treated with wool fat plus ultraviolet irradiation. In group 2 are those patients in whom there was a definite increase in the lipids after treatment, while in group 3 are those in whom there was no appreciable change in lipids. After twenty treatments with wool fat and ultraviolet irradiation, a patient in group C (case no. 67,886), starting with a fifteen minutes' exposure to ultraviolet rays, failed to show a significant rise in the cholesterol of the blood serum; there was no change in the other lipid constituents. It is of interest to note that in this instance the initial lipid values were within normal limits. All of the other cases in this group showed definite increases in cholesterol values as follows: 37 mg. in no. 67,298, 105 mg. in no. 4,402, 47 mg. in no. 67,413, 53 mg. in no. 60,490 and 29 mg. in no. 59,805. In those cases in which all of the lipid fractions were determined, the increases in free cholesterol were respectively 28 mg., 30 mg. and 20 mg., while the increase in cholesterol esters was 29 mg., 30 mg. and 20 mg. There was also a rise in the total alcohol ether extract of 40 mg., 100 mg. and 320 mg. In no case was there an alteration in the lipoid phosphorus. In the five cases in which a significant rise in the lipids occurred, the patients had a low initial blood serum cholesterol concentration. With one exception (no. 60,490), after the patients had received inunctions of wool fat and ultraviolet irradiation, the blood serum cholesterol rose to a normal level. The exception showed a blood cholesterol after treatment of only 125 mg., which nevertheless was a rise of 59 mg. over the initial figure.

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Values in Group C.—Group 1: The fourteen patients in this subdivision showed a marked rise in the lipid constituents. The initial cholesterol varied between 48 and 150 mg., with ten patients having 115 mg., or less, and only one having a normal figure (150 mg.). After treatment, the cholesterol varied between 150 and 230 mg., the actual increase in cholesterol concentration varying between 25 and 178 mg., the average being 90 mg. In these cases the cholesterol was still within a normal range of values one year after the last treatment, with the exception of cases no. 59,369 and no. 20,772, in which the final determinations of cholesterol were 127 and 125 mg.

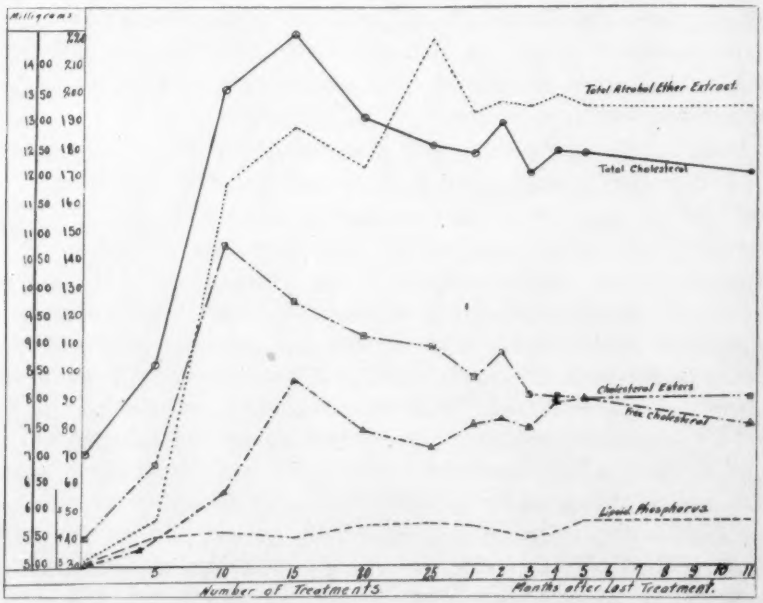

Chart 1 (case no. 21,868).—Typical changes in the values for lipids after treatment with inunctions with wool fat and ultraviolet irradiation. The column of figures on the extreme left-hand side of the chart represent milligrams of the total ether extract; those in the intermediate column, milligrams of lipoid phosphorus, and those in the third column, milligrams of the free, total and cholesterol esters per hundred cubic centimeters.

Observations of the other lipids in which such determinations were made showed that in ten cases the free cholesterol rose from 8 to 57 mg., the average being 34.4 mg. In nine patients in this group, the increase was over 16 mg. The cholesterol esters were increased in all ten, the increase varying between 15 and 108 mg. In nine out of the ten patients, the rise was higher than 32 mg. The total alcohol ether extract also showed a rise in twelve cases, varying between 60 and

930 mg., with an average of 487 mg. The smallest increase (60 mg.) was found in case no. 4,403, in which the lipids were within normal limits before treatment was started. Nine of the ten cases showed an increase of over 200 mg. The lipoid phosphorus changed little after treatment. The variations ranged between 0.1 and 1.8 mg., the average being 0.9 mg. However, in nine of the twelve cases, the rise was between 0.7 and 1.8 mg. Chart 1 (case no. 21,868) shows the typical lipid changes as observed after treatments with inunctions of wool fat followed by ultraviolet irradiation.

Group 2: No significant changes in the lipids occurred in seven cases in which inunctions of wool fat and ultraviolet irradiation were given. Four of these patients showed an initial normal blood serum

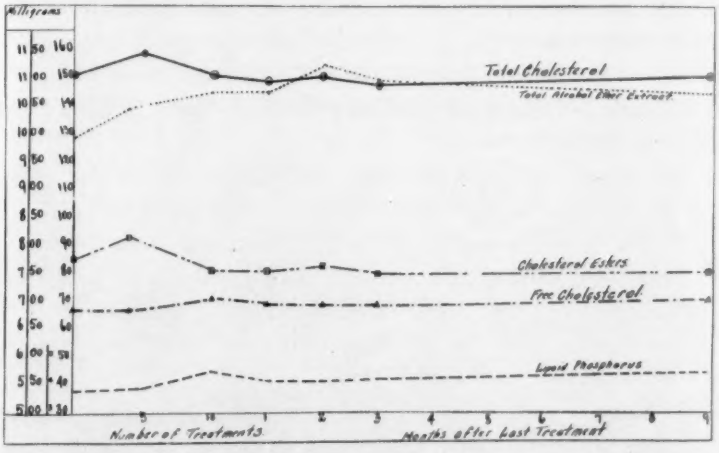

Chart 2 (case no. 23,357).—Values found in group in which changes in the lipid content did not occur following treatment with inunctions with wool fat and ultraviolet irradiation. (Compare with chart 1).

cholesterol concentration. The remaining three showed an initial cholesterol content of 100, 115 and 125 mg., respectively. After treatment, there was no definite rise in any of the lipid fractions. The only exception was case no. 66,581, in which the lipoid phosphorus increased only 1.6 mg. Chart 2 (case no. 23,357), showing the changes which are typical of this group, is given for comparison with chart 1.

SUMMARY

The blood lipids of sixty-seven patients were studied; of these thirty-five had an initial blood serum cholesterol within the normal range, and were used as normal controls. Thirty-two patients were treated as follows: group A, ultraviolet irradiation alone; group B,

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inunctions with plain wool fat followed by inunctions with irradiated wool fat; group C, inunctions of wool fat followed by ultraviolet irradiation.

In group A, two of the eight patients who received only ultraviolet treatment showed a rise in lipids. In the six cases in which the patients showed no change with irradiation alone, a substantial increase in the lipids occurred after inunctions with wool fat and ultraviolet irradiation.

In group B, there was no rise in lipids after inunctions of plain wool fat, but definite increases were obtained after the use of irradiated wool fat.

Nineteen patients in group C had a low initial cholesterol concentration; seventeen of them showed a substantial rise in lipids after treatment. Of six cases with normal initial lipid figures, only two showed a rise after treatment.

CONCLUSIONS

1. Ultraviolet irradiation increased the blood lipids in 25 per cent of the patients studied.

2. Treatment by inunction with nonirradiated wool fat produced no changes in blood lipids; however, subsequent treatment with irradiated wool fat definitely increased the lipid fractions of the blood.

3. Treatment with inunctions with wool fat followed by ultraviolet irradiation produced significant increases in blood lipids in 89 per cent of the cases with a low initial cholesterol, and in 33 per cent of the cases with a normal initial cholesterol.

4. Treatment with wool fat and ultraviolet light also produced a rise in free cholesterol and cholesterol esters in 86 per cent of the cases, and of the total alcohol ether extract, in 91 per cent of the cases in which this treatment was given.

5. Of ten cases in which a low initial value for lipoid phosphorus was encountered, none showed a rise in lipoid phosphorus after treatment with wool fat and ultraviolet irradiation.

6. Low values for cholesterol are an indication as to the necessity for treatment with inunctions with wool fat and ultraviolet irradiation. Changes in the amount of cholesterol serve as a guide to the amount of treatment to be given.

THE NORMAL HISTOLOGY OF INFANTS' BRAINS

WITH PARTICULAR REFERENCE TO ANATOMIC CHANGES IN THE BRAIN IN INTESTINAL INTOXICATION OF INFANTS *

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Intestinal intoxication of infants, or so-called toxicosis of infants, is a fairly well recognized clinical entity. Its etiology, however, is still obscure. Recently, in the light of the modern conception of the hypothalamus as the seat of centers regulating vegetative functions, an attempt was made by Goldzieher [1] to trace the extreme dehydration that characterizes this disease to pathologic alterations in the brain, particularly in parts of the diencephalon adjacent to the floor and walls of the third ventricle. He reported three cases of intestinal intoxication, in which he believed he found definite inflammatory lesions in the hypothalamic and paraventricular regions as well as in the midbrain. The lesions were described by him as diffuse and nodular infiltrations, "scattered all over the hypothalamus and the brain tissue around the tuber cinereum, being most conspicuous in the gray matter surrounding the third ventricle." The nodules varied in size in accordance with their cellular contents, assuming at times large dimensions, numbering more than 100 cells. The latter he considered to be mainly glial in type. Among the cells, he noted also occasional polymorphonuclear leukocytes He assumed that these nodular and diffuse cellular accumulations were inflammatory, and he regarded them as "gliosis" and leukocytic infiltrations. This view was further strengthened by his observation of an "interstitial exudation" that caused the brain tissue to become honeycombed about some of the nodular foci. He found in the same regions nerve cells that were shrunk and poorly staining, with some in the process of disintegration (neuronophagia). Because of the selectively localizing character of the disease process, Goldzieher drew an analogy

* Submitted for publication, July 6, 1931.

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1. Goldzieher, M.: Ueber encephalitische Gehirnveränderungen bei sogenannter Exicosse, Klin. Wchnschr. **9**:981 (May 24) 1930; Encephalitic Changes in So-Called Toxicosis of Infants, Am. J. Dis. Child. **40**:446 (Aug.) 1930.

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between this disease and poliomyelitis, which, in turn, he regarded as further proof of the inflammatory character of the cellular infiltrations he described in his material.

These observations led him to assume that alimentary toxicosis is a condition caused by a form of encephalitis in which the inflammatory process is limited to the tuber cinereum and adjacent parts of the diencephalon. Since the latter, according to present beliefs, contain, among other centers that control vegetative function, also a center for the regulation of water metabolism, he reached the conclusion that a lesion in this location may account for the extreme dehydration in alimentary toxicosis. With this in mind, he proposed for this disease the term "diencephalitis dehydrans" to indicate that an inflammatory lesion in the diencephalon, provoking a disturbance in water metabolism, causes the dehydration, which is the outstanding symptom in the clinical picture.

The histologic descriptions and the photomicrographs that illustrated Goldzieher's findings,[2] when analyzed in the light of knowledge of the normal structure of the brain of an infant, led us to believe that he interpreted as inflammatory lesions cellular aggregations that are normal morphologic features in infants' brains. Spielmeyer,[3] Schob [4] and others have repeatedly called attention to the frequency with which faulty deductions are drawn from incorrect observations made on infant brain material. The reason for such errors is readily understood when it is realized that the human brain does not mature at the time of birth, that the ripening process goes on for years during the postnatal life of the patient, and that it is difficult to say when the process of differentiation ends. Certain it is, however, that the ripening process of the central nervous system is in progress during the early years of postnatal life, and that in this process, under normal conditions, cell migration for purposes of final topographic cell distribution is a very important event. It is known that this cell migration proceeds from the subependymal zone into the more peripheral areas of the central nervous system; hence, to find large cell accumulations in paraventricular zones is not surprising, unless discovered in the fully matured brain, when they constitute a form of malformation and fall into the category of so-called heterotopias. In the diencephalon, the organization of centers makes large demands for cellular material; because of this, the subependymal cell groupings are correspondingly large. These

2. Goldzieher (footnote 1, first reference).

3. Spielmeyer, W.: Handbuch der Geisteskrankheiten, Spezieller Teil VII: Die Anatomie der Psychosen, Berlin, Julius Springer, 1930.

4. Schob, F.: Pathologische Anatomie der Idiotie, in Spielmeyer (footnote 3, p. 779).

cells often aggregate about blood vessels in the form of small spherical groups or linear tracts, and are often erroneously considered evidence of inflammation. Such cell distribution is readily explained when it is recognized that abundant provision of a blood supply is essential to actively proliferating cells. These are but a few of the conditions one must guard against in interpreting findings in the central nervous system of the infant. One who is not familiar with the topography of an infant's brain may easily err in evaluating such features, and may make grievous mistakes.

Our aim in this contribution is to report the histologic observations in a group of fatal cases of intestinal intoxication (nine cases) and to present our views, as opposed to those expressed by Goldzieher, on the probable existence in the brain of lesions pathognomonic of this disease. In order to provide a firm basis for the interpretation of our findings, we undertook the study of a large number of normal brains of infants, and we have compared the anatomic features in the normal brain with those in the brains of infants who have died of intestinal intoxication. Thus, before offering the protocols of the nine cases of well established instances of intestinal intoxication, we shall first present our findings in normal material.

MATERIAL AND METHODS

The material for this study consisted of thirty-three brains (see accompanying table) obtained from infants who died as a result of some systemic disease and were free during the clinical course from any evidence of intestinal intoxication; eight brains were from infants who died of fatal alimentary intoxication and one from an infant who, having recovered from an initial attack of intestinal toxicosis, succumbed later to bronchopneumonia. The brains in the first group (see table) are regarded as normal, since during life they manifested no signs pointing to disease of the central nervous system, and on careful microscopic examination disclosed no histologic alterations. They are employed to establish the basis for the interpretation of the findings in the second and third groups and to reveal normal variations in the cellular topography of the brains of infants.

The gross material was fixed as a routine in 20 per cent formaldehyde. After thorough hardening, the brains were sectioned, the blocks being taken uniformly from several regions: (1) the diencephalon, ventral and dorsal to the floor of the third ventricle, including the tuber cinereum and the mamillary bodies, extending for short distances laterally; (2) the cerebral cortex; (3) the mesencephalon and (4) occasionally the cerebellum and the medulla. Most of the blocks were embedded in celloidin and some in paraffin, and some were left unembedded for the preparation of frozen sections. The celloidin blocks of the hypothalamus were sectioned serially (15 microns thick) and stained by the Nissl method, with

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Case	Age	Clinical Features	Necropsy Observations
1	5 months, premature	Stillborn	Hemorrhage in subcutaneous tissue of scalp
2	6 months, premature	Died shortly after admission	Patent ductus arteriosus and foramen ovale
3	7 months, premature	Died shortly after admission; lived 2 hours	Atelectasis of both lungs
4	7 months, premature	Roentgen abortion	Ascites; petechial hemorrhages in pericardium, suprarenals and lungs
5	7 months, premature	Lived 6 hours	Atresia ani; double bicornuate uterus with double vagina; patent foramen ovale; absence of gallbladder
6	7 months, premature	Died shortly after admission; lived 36 hours	Atelectasis (both lower lobes); patent foramen ovale
7	7 months, premature	Jaundice; lived 7 days	Patent foramen ovale; congestion of viscera
8	7 months, premature	Infection (?); lived 49 days	Bronchopneumonia
9	36 hours	Hemorrhagic disease of the new-born (?)	Hemorrhages into peritoneum, stomach, pleural cavity, lungs and pericardium; subdural hemorrhage; tentorial tear
10	3 days	Developmental defect of genito-urinary tract (see necropsy observations)	Extrophy of bladder with epispadias; communication between ileum, cecum and bladder; imperforate anus; pyelonephritis; subpial hemorrhage
11	3 days	Bronchopneumonia; jaundice	Bronchopneumonia
12	5 days	Bronchopneumonia	Bronchopneumonia; hypertrophy and dilatation of right ventricle
13	6 days	Birth hemorrhage (?); atelectasis at base of lungs	Atelectasis of lungs; dilatation of right auricle and ventricle; acute congestion of viscera; subarachnoid hemorrhage
14	8 days	Marasmus; bilateral otitis media	Marasmus; bilateral purulent otitis media; patent ductus arteriosus
15	2 weeks	Malnutrition	Malnutrition
16	2 weeks	Bronchopneumonia	Bronchopneumonia
17	1 month	Generalized edema; malnutrition; congenital syphilis	Pneumonia; parenchymatous degeneration of heart, liver, kidneys, intestines and spleen
18	40 days	Meningitis (?)	Nodose syphilitic infiltration of lungs, pancreas and liver; subarachnoid hemorrhage (microscopically)
19	40 days	Bronchopneumonia	Bronchopneumonia; fatty degeneration of liver; parenchymatous degeneration of kidneys; slight subpial hemorrhage
20	40 days	Acute infection	Marasmus; aberrant pancreas
21	6 weeks	Marasmus; gastro-enteritis; bilateral otitis media	Gastro-enteritis; marasmus; bronchopneumonia; patent ductus arteriosus; bilateral purulent otitis media
22	7 weeks	Intestinal intoxication (?)	Follicular ulceration of Kundrat; bronchopneumonia (?); parenchymatous degeneration of heart, liver and kidneys; congestion of viscera
23	2 months	Brain injury or idiocy (?); severe anemia secondary to gastro-intestinal bleeding	Two peptic ulcers of duodenum and smaller ulcer of esophagus; aspiration of blood into lungs
24	2 months	Malnutrition; bilateral otitis media	Bronchopneumonia; parenchymatous degeneration of liver; acute splenic tumor
25	2 months	Pneumonia	Bronchitis with atelectasis of lungs; left otitis media; cysts in ovaries; gross convolutional anomalies; no histologic alterations
26	2 months	Malnutrition	Ulceration of tongue (thrush); rickets; marasmus; pulmonary edema; noduli albini on tricuspid valves; hemorrhage into suprarenals; subarachnoid hemorrhage (agonal)
27	3 months	Rickets (tetany?); bronchopneumonia	Acute bronchitis; early bronchopneumonia
28	5 months	Bronchopneumonia	Bronchopneumonia; parenchymatous degeneration of liver and kidneys; lymphoid hypertrophy of small intestines and to a less degree of large intestines
29	5 months	Bronchopneumonia	Pulmonary edema and congestion; parenchymatous degeneration of liver; hyperplasia of thymus
30	8 months	Mental deficiency (?); bronchopneumonia	Bronchopneumonia; parenchymatous degeneration of heart, liver and kidneys
31	8 months	Mental deficiency (?); otitis media	Bilateral otitis media; congestion of lungs, intestines and spleen; bronchopneumonia; fatty liver
32	14 months	Rickets; terminal bronchopneumonia	Rickets; terminal bronchopneumonia
33	3 years	Enterocolitis; typhoid fever (?); ruptured appendix (?)	Diffuse ulcerative enterocolitis; perforation of ulcer of appendix; pyelonephritis; cystitis

hematoxylin-eosin and iron hematoxylin. The paraffin blocks were sectioned 7 microns in thickness and stained with hematoxylin-eosin. The frozen sections were stained with the silver carbonate method of Hortega, as modified by Globus.[5]

OBSERVATIONS ON HISTOLOGIC FEATURES IN THE BRAINS OF INFANTS

The Cellular Aggregations in the Hypothalamus and in Regions Adjacent to the Walls of the Third Ventricle.—Circumscribed accumulations of deeply staining cells are frequently found in the hypothalamus and the paraventricular areas in brains of infants and young children. These cellular accumulations usually form compact cellular masses (fig. 1 *A*), which assume various outlines: round, oval, oblong or irregular (figs. 1 *B* and 2 *B* and *C*). Occasionally they are somewhat diffuse and poorly demarcated from the adjacent areas less densely populated with cells (fig. 1 *B*). In many instances the cells are aggregated about a central or a somewhat eccentric vessel and assume a cuff-like arrangement (fig. 2 *A*), not unlike that seen in inflammatory lesions of the brain. The cells occasionally assume a linear orientation in regions where fibrous tracts are forming (fig. 3 *A*).

These cellular aggregations, which may be regarded as germinal centers, are recognized early in the development of the central nervous system. In our material they were already noted in the sixth month of fetal life and could be followed up to 3 years of postnatal life. As the age of the person advances, the size of these areas and the density of their cellular contents become less marked.

The character of the cells that form these compact collections is less clearly identified. The impression gained is that they are glial in character. Occasionally, there are noted within such groups more ripened elements (fig. 3 *B*) that have the character of developing neuroblasts.

Silver-stain methods aid somewhat in identifying these cells, for they disclose at the periphery of the germinal areas well formed astrocytes that seem to arise in and to migrate from the dense groups of undifferentiated cells.

Not unlike the perivascular arrangement of undifferentiated glia cells, developing nerve cells are found forming irregularly around areas about blood vessels or assuming a linear orientation parallel to the direction of a long vessel (fig. 3 *C*).

The Subependyma.—The subependymal zones in the brain of the young also show vast accumulations of cellular elements. It is com-

5. Globus, J. H.: The Cajal and Hortega Glia Staining Methods: A New Step in the Preparation of Formaldehyde-Fixed Material, Arch. Neurol. & Psychiat. **18**:263 (Aug.) 1927.

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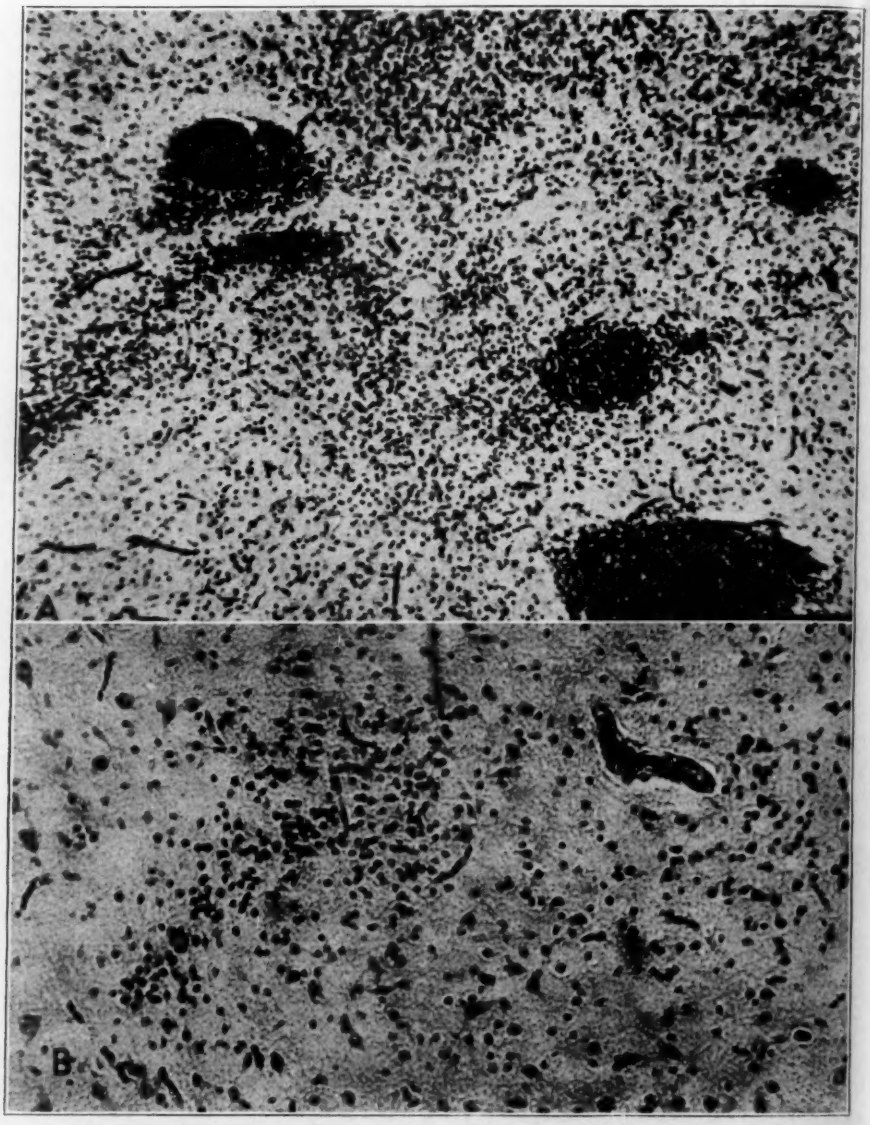

Fig. 1.—*A*, nodular collections of deeply staining cells (germinal centers) in the tuber cinereum of a 7 month fetus. Hematoxylin-eosin stain; × 200. *B*, similar nodules, less discrete, in a 6 month fetus. Hematoxylin-eosin stain; × 300.

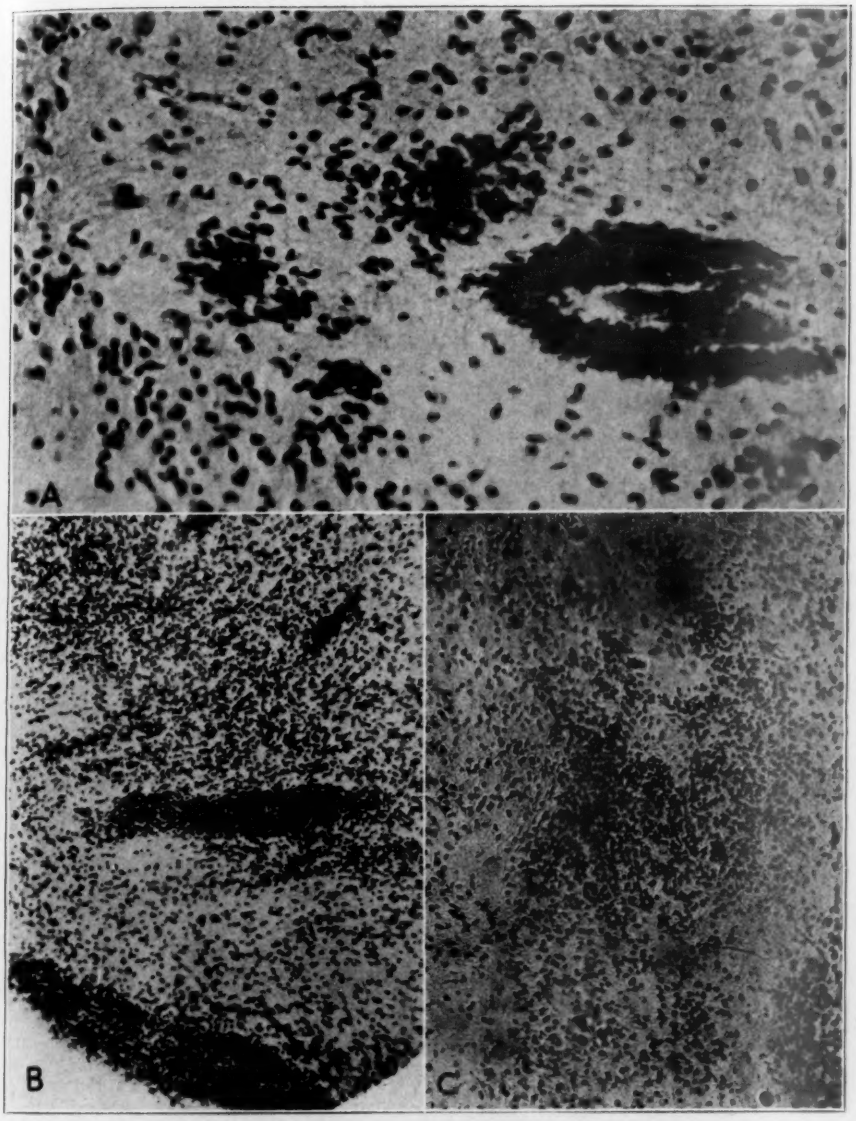

Fig. 2.—*A*, undifferentiated germinal cells in nodules or rings collected about blood vessels in a way simulating perivascular infiltration; from the hypothalamus of a 5 day old infant. Hematoxylin-eosin stain; × 390. *B*, elongated nodular collections in the hypothalamus of a 5 day old infant. Hematoxylin-eosin stain; × 140. *C*, less dense cellular aggregations in the hypothalamus of a 5 day old infant. Hematoxylin-eosin stain; × 140.

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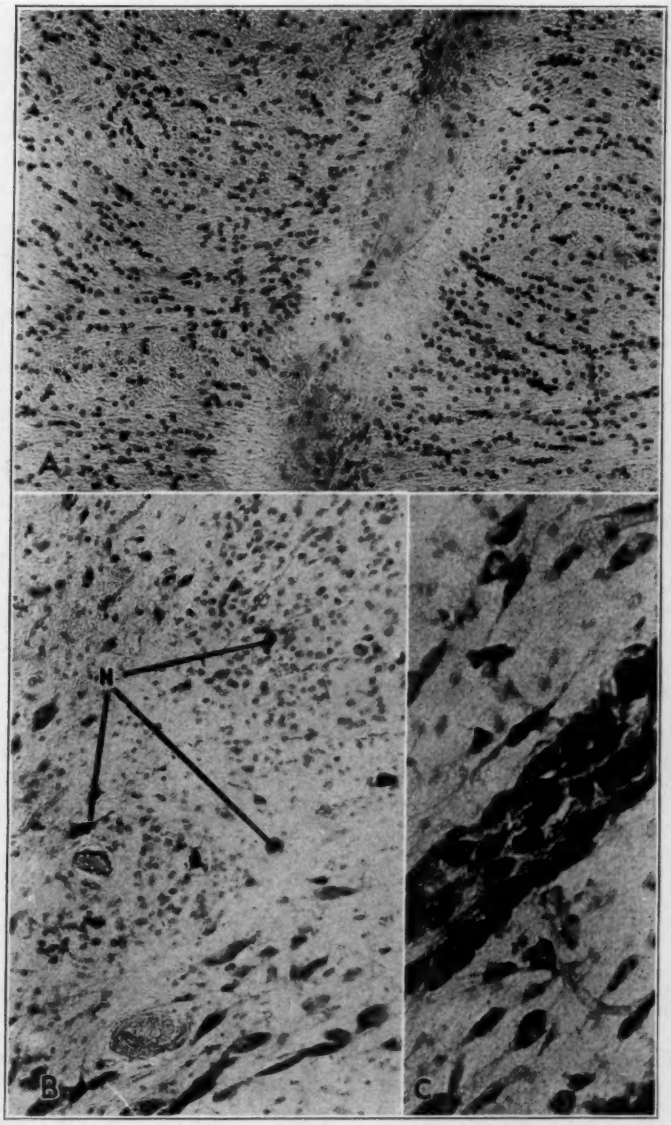

Fig. 3.—*A*, linear orientation of glia cells in the region of a forming tract in the hypothalamus of a child 3 years old. Hematoxylin-eosin stain; × 170. *B*, differentiating nerve cells (*N*) in a germinal center; from the hypothalamus of a 1 year old child. Toluidine blue stain; × 170. *C*, nerve cells in linear orientation; from the hypothalamus of a 10 day old infant. Toluidine blue stain; × 350.

monly believed that these cells are glial in character. However, special staining methods do not reveal definitely their true glial character; neither can one recognize well defined neuroblasts in these areas. It is more correct to say that these cells are undifferentiated neuro-ectodermal elements. Such cellular accumulations in the subependymal zone are arbitrarily referred to as subependymal gliosis. This so-called subependymal gliosis varies in the density of its cellular elements, in depth and in the uniformity of distribution. In the fetal brain such subependymal masses are often so large and dense as to give the impression of tumor formation (fig. 4 *A*). In a later stage, the subependymal gliosis acquires a more uniform distribution and becomes progressively

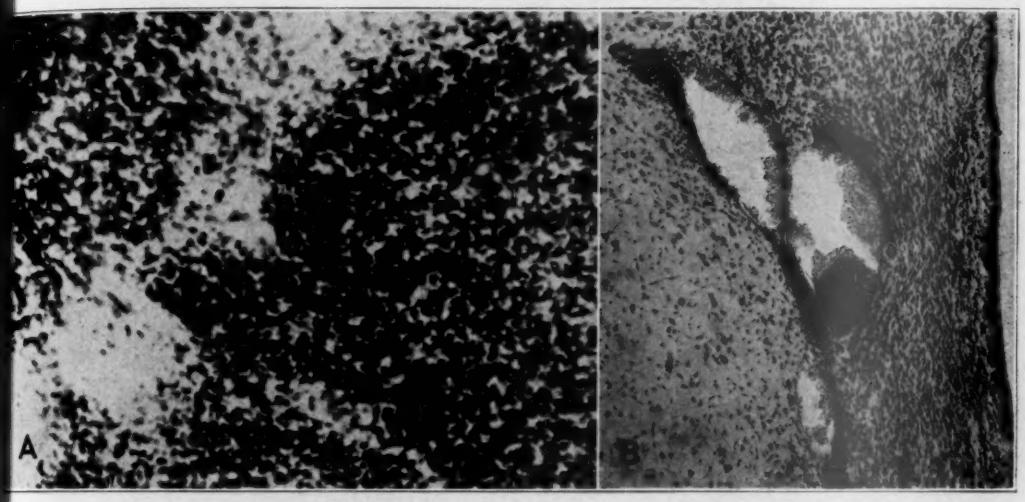

Fig. 4.—*A*, subependymal zone in the wall of the third ventricle of 7 month fetus. Hematoxylin-eosin stain; × 340. *B*, subependymal zone in the wall of the third ventricle of a 40 day old infant. Toluidine blue stain; × 150.

narrower (fig. 4 *B*). Within this subependymal zone also cells are often arranged about blood vessels in a way to give the erroneous impression of an inflammatory process (fig. 5 *A*). Circumscribed, round areas of relative rarefaction are often seen (fig. 5 *B*) in foci in which tracts are in the process of formation, and may give the false impression of a degenerative process.

The Pia-Arachnoid.—It is well known that the pia-arachnoid in the very young does not present the clear cleavage between its component membranes: the pia and the arachnoid. The separation becomes more and more definite as time goes on, but apparently the process of splitting is not chronologically uniform throughout the extent of the pia-

arachnoid, as there are areas in which the cleavage is normally delayed and the embryonal character of the meninges is retained for a longer period than in other parts.

In the interpeduncular space, about the tuber cinereum, the pia-arachnoid apparently retains the embryonal character of the meninx for a longer time. In the fetal brain the meninx is a fairly dense mesodermal structure, with no indication of a split (fig. 6*B*), while at a later stage, as in the 3 day old infant, it begins to show signs of rarefaction and assumes a mesenchymal character that is most likely

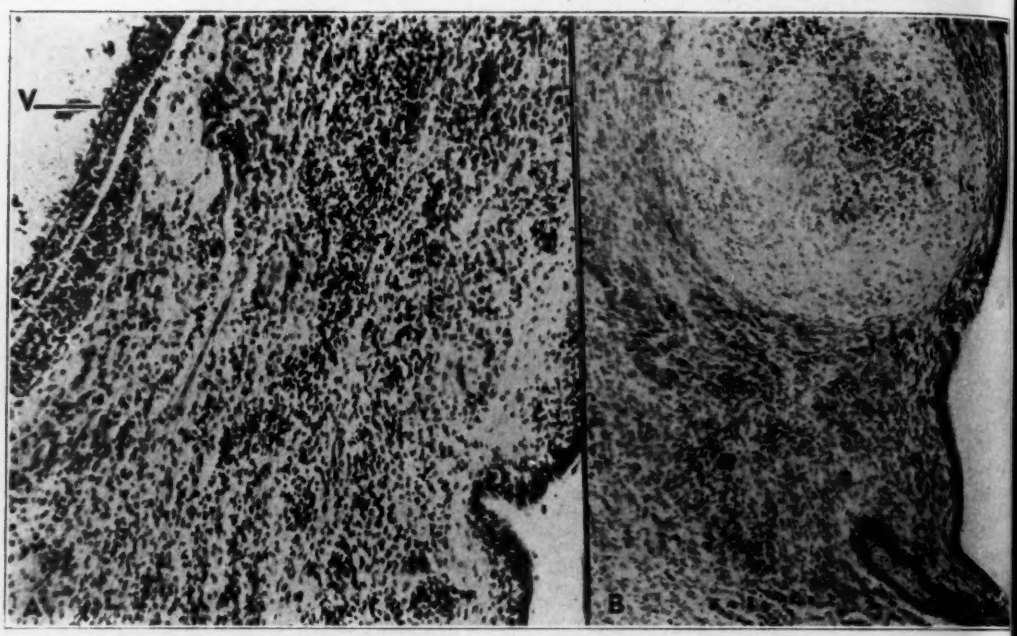

Fig. 5.—*A*, subependymal zone, densely populated with cells, showing at the upper left corner a vessel (*V*) surrounded by a denser zone of cells, simulating an inflammatory lesion; from the wall of the third ventricle of an infant 36 hours old. Hematoxylin-eosin stain; × 200. *B*, subependymal zone, showing a circumscribed area of rarefaction at the site of a developing tract; from the wall of the third ventricle of an infant 40 days old. Toluidine blue stain; × 150.

preparatory to further cleavage (fig. 6*A*). The fibrous appearance of the pia-arachnoid in the infant may also mislead by giving the impression of a chronic inflammatory lesion. At about the sixth week of postnatal life, the pia again acquires a different character. Here the cells are of an epithelial type arranged in several layers (fig. 7). Another interesting feature in the pia-arachnoid of the infant that may be erroneously interpreted as a pathologic condition is the presence in

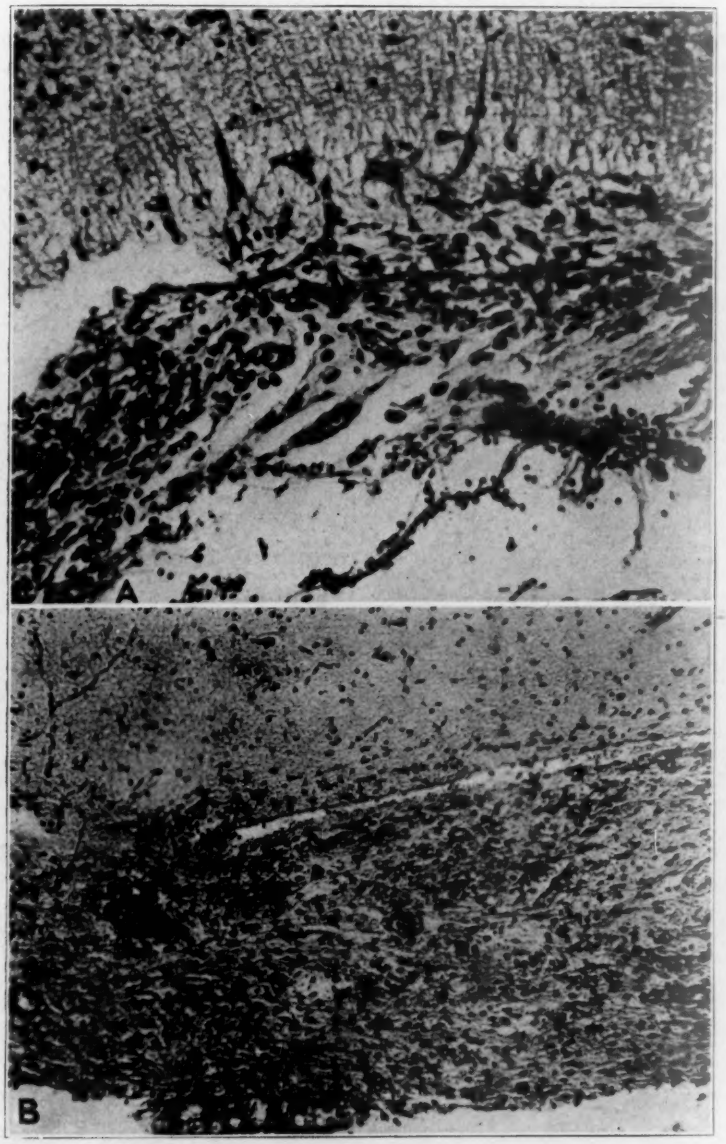

Fig. 6.—*A*, leptomeninges in the interpeduncular space of a 3 day old infant. Hematoxylin-eosin stain; × 310. *B*, leptomeninges in the interpeduncular space of a 6 month fetus. Hematoxylin-eosin stain; × 200.

the region of the interpeduncular space of areas in which large numbers of microglia seem to migrate from the pia into the brain tissue (fig. 8), constituting the so-called microglial fountain of Hortega.[6]

The Tuber Cinereum and Its Blood Vessels.—Another feature found in the tuber cinereum that deserves mentioning, as it may be a frequent source of error, is the presence of peculiarly constructed blood vessels. These vessels are seen entering the tuber cinereum from its pial lining

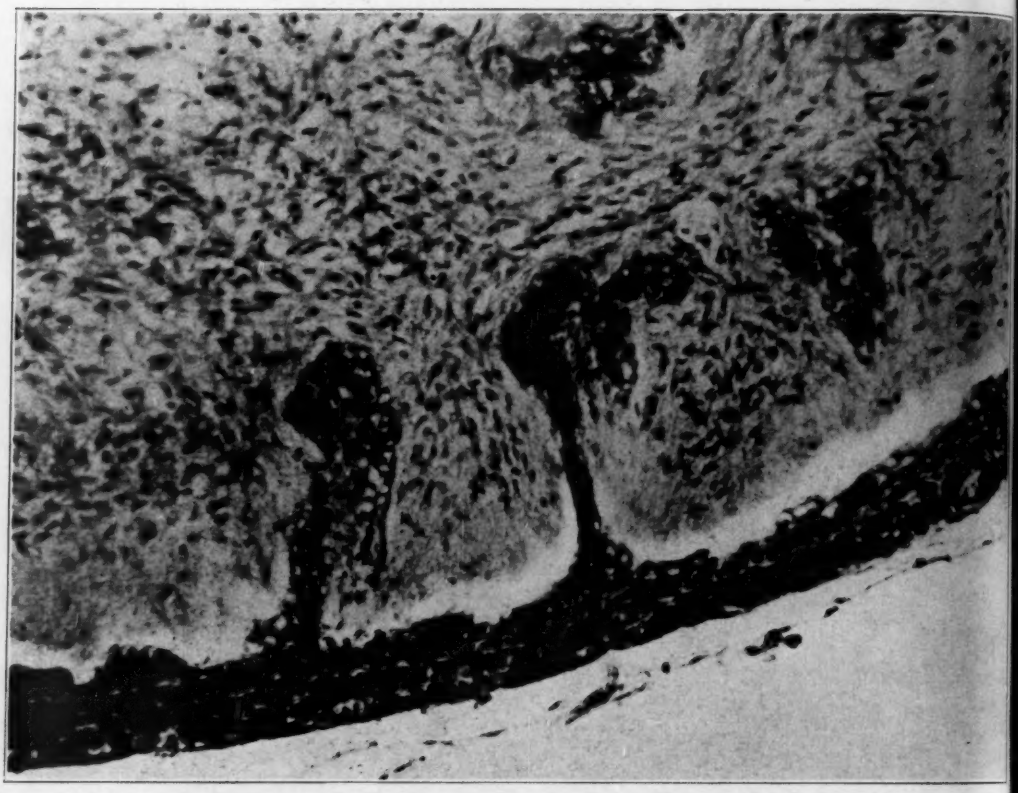

Fig. 7.—The pial covering of the tuber cinereum in an infant 6 weeks old. Hematoxylin-eosin stain; × 280.

as large trunks that branch out into smaller vessels (fig. 9). All of these vessels appear as large sinuses lined by a single layer of endothelial cells, which in turn is surrounded by a wide zone consisting of a meshwork of fine fibers and a few nuclei (fig. 10). This peculiar

6. Hortega, quoted by Penfield, W.: The Interstitial Tissue of the Central Nervous System, in Cowdry, E. V.: Special Cytology, New York, Paul P. Hoeber, Inc., 1928, vol. 2, p. 1032.

vascularization of the tuber cinereum and the unique vessel pattern were noted in maturing brains up to the fifth year of postnatal life. Three brains were studied in later stages, the ages of the patients being 17, 25 and 28 years. In these the vessels, though still retaining some similarity to the general pattern, showed definite alterations in the vessel walls and the contiguous tissue. The vessels had assumed a more

Fig. 8.—The microglia fountain of Hortega (*Mic.*) at the base of the tuber cinereum in a 6 day old infant. Globus modification of Hortega's silver carbonate method; × 340.

mature character, the zone of fine fibrillary meshwork having been replaced by a narrow rim of dense fibrous material. They were of smaller caliber, showed less branching and were surrounded by a rich glial network.

Glia.—The presence of large numbers of glial elements in the white matter of an infant's brain has often been interpreted as evidence of

a pathologic process. Thus, Virchow,[7] finding large numbers of fat-containing glia cells in the infant's brain, was led to recognize an inflammatory disease in the new-born. He named it encephalitis neonatorum, and thought that the cause was transmitted by the mother during the

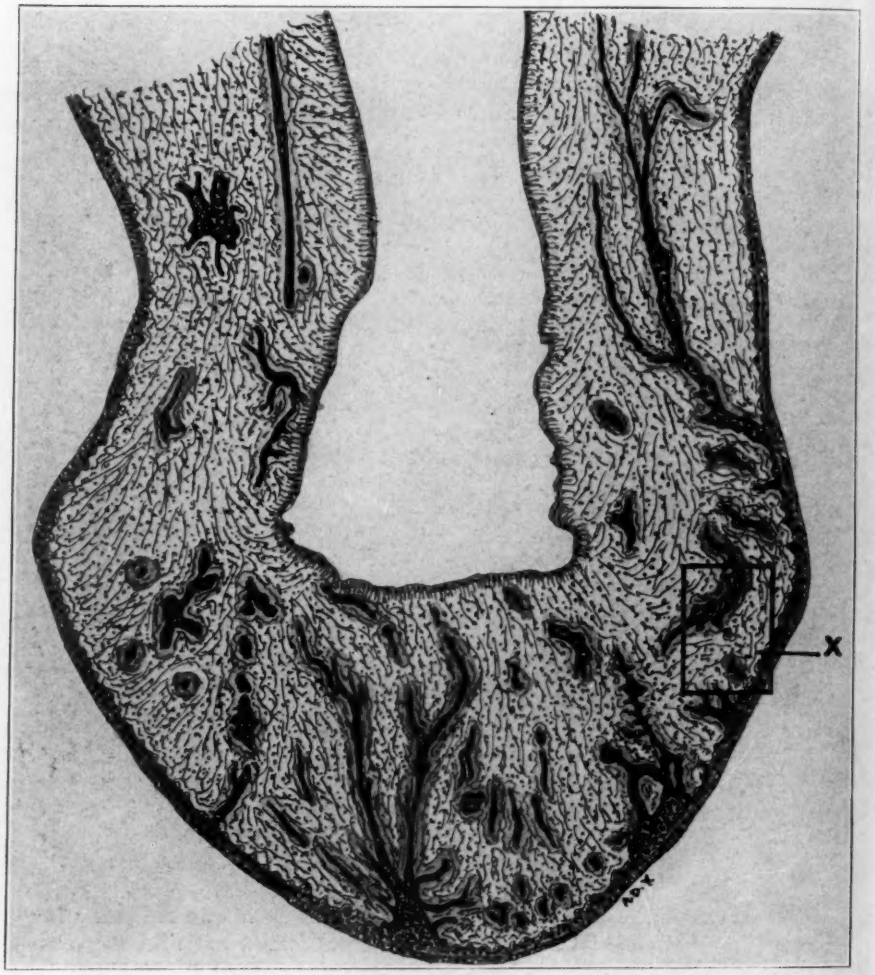

Fig. 9.—Drawing of a section of the tuber cinereum, showing its peculiar vascularization, in a 5 months old infant. The section marked *X* is shown in figure 10.

period of gestation. Jastrowitz,[8] later, studying a large number of infants' brains, found similar gliosis in the normal brain of the new-

7. Virchow, R.: Kongenitale Encephalitis und Myelitis, Virchows Arch. f. path. Anat. **38**:129, 1867; Ueber interstitische Encephalitis, ibid. **44**:472, 1868.

8. Jastrowitz, M.: Encephalitis und Myelitis des ersten Kindesalters, Arch. f. Psychiat. **2**: 389, 1869-1870; **3**:162, 1871-1872.

Fig. 10.—A vessel (*B.V.*) in the tuber cinereum, taken at *X* in figure 9. *P* indicates the pial membrane. Hematoxylin-eosin stain; × 390.

born and regarded the gliosis as a normal physiologic condition. He thought that the glia in the new-born is concerned with the elaboration of material essential to the growing nervous system. Thus, in our material, astrocytes were found in fairly large numbers in the subcortex (fig. 11), but are not to be regarded as of pathologic origin.

Fig. 11.—Astrocytes in the subcortex of a 6 day old infant. Globus modification of Hortega's silver carbonate method; × 300.

SUMMARY OF THE ANATOMIC OBSERVATIONS ON NORMAL BRAINS OF INFANTS

The description of some of the histologic features found in the maturing human brain is not intended as a full account of the histogenetic processes that take place in the ripening brain. It is desired to draw attention to a few normal histologic alterations that often serve as a source of error. It is obvious from the accompanying illustrations and the description of the anatomic observations on normal brains of

infants that well circumscribed and somewhat less demarcated focal accumulations of deeply staining cells are a common occurrence. They represent, as already noted by many competent observers, ontogenetic and histogenetic phases in the development of the normal architecture of the brain, and may be considered as germinal centers. Caution must

Fig. 12 (case 1).—Excessively distended blood vessels in the cerebellum. Iron-hematoxylin stain; × 200.

be exercised in interpreting such nodular accumulations of cells because of their superficial resemblance to focal nonsuppurative inflammatory lesions in the central nervous system.

REPORT OF CASES

CASE 1.—*History.*—M. R., a girl, aged 10 days, was admitted to the Mount Sinai Hospital on July 22, 1930. She was breast-fed for one day, and then artificially fed on whole milk, water and dextrimaltose. She began to vomit on

the day the formula was begun, and continued to do so until admission to the hospital. There were from four to six stools a day until the day before admission, when she had twelve bowel movements. The stools were very watery and yellow.

Examination.—The patient appeared very toxic; her respirations were rapid and deep (Kussmaul breathing). The temperature was 102.5 F. The skin turgor was very poor, and there was extreme dehydration. Abdominal peristalsis was noted. An indefinite mass was felt in the upper part of the abdomen.

Course.—Because of the peristalsis and the vague abdominal mass, stenosis or spasm of the pyloris was considered first, but intestinal intoxication was regarded as the more likely diagnosis. The infant was given a serum transfusion, and a continuous intravenous drip of 5 per cent dextrose in saline was administered during thirty-three hours with fair results. The stools became less numerous, and the child was able to retain small amounts of fluid. The temperature continued elevated at times, and ranged between 99 and 102 F. The skin turgor remained poor, and the breathing continued to be labored. The continuous intravenous drip was resumed, and the child received an additional 220 cc. of 5 per cent dextrose in saline. A transfusion of whole blood was begun, but the patient died suddenly after 40 cc. of blood had been given.

Necropsy Observations.—Thoracic and Abdominal Organs: The peritoneal and pleural cavities contained moderate amounts of fluid. The thymus looked fleshy and markedly edematous. The heart showed a flabby myocardium and a markedly dilated right ventricle. The ductus botalli and foramen ovale were patent. The lungs showed bronchopneumonic patches. The liver and spleen were very flabby. The gastro-intestinal tract appeared congested. The kidneys showed parenchymatous degeneration.

Brain: The brain showed marked congestion of the pial blood vessels, especially over both temporal poles, but no other gross anatomic alterations. Microscopic examination revealed no inflammatory or degenerative changes. The cellular aggregations in the gray matter about the third ventricle and the hypothalamus showed the same topographic distribution as in the normal brain of the corresponding age.

The pial vessels were tremendously distended (fig. 12) and simulated the picture of an injected brain specimen. It was very likely caused by the intravenous therapy. In the midbrain, aside from distention of the blood vessels, there were no alterations, inflammatory or degenerative.

CASE 2.—*History.*—R. B., a boy, aged 3 months, was admitted to the Mount Sinai Hospital on Aug. 9, 1929. Two days before admission he became restless, cried considerably and began to have loose stools. The next day, he began to vomit profusely after each feeding.

Examination.—The infant was acutely ill, poorly developed and poorly nourished. The anterior fontanel was depressed. His eyes rolled from side to side. There was a marked loss of tissue turgor. The right ear was normal. The left ear-drum was red and thick; there was no postauricular tenderness or edema. Examination of the blood showed: hemoglobin, 90 per cent; red cells, 4,200,000; white cells, 13,000; polymorphonuclear leukocytes, 69 per cent, and lymphocytes, 31 per cent.

Course.—The infant was not fed for six hours, but was given a transfusion and hypodermoclysis. Small feedings were then begun. They were kept at a low level and were supplemented by subcutaneous injections. On the third day after admission, the left ear was opened, and a thin exudate obtained. At about the

same time, signs of pneumonia developed. Two days later the right ear-drum was also opened, and a purulent discharge obtained. The temperature ranged from 99 to 104 F. On the sixth day after admission, the child died.

Necropsy Observations.—Thoracic and Abdominal Organs: The heart showed intense capillary congestion. The lungs showed congestion of the left lower lobe. The liver was slightly enlarged and flabby, but showed no histologic alterations. The spleen was markedly congested. The stomach was distended with gas and greenish fluid. The entire intestinal tract was distended and contained brownish fluid. There were no ulcerative lesions. The kidneys showed marked tubular degeneration. The suprarenals showed hemorrhages in the medulla and decreased lipoid content of the cortex. Both middle ears and ethmoid sinuses contained a purulent exudate.

Brain: The longitudinal and the lateral sinuses and the pial vessels on the convexity of the brain were filled with marantic thrombi. There was, in addition, a widespread extravasation of blood in the subarachnoid space, particularly over the right frontal lobe (agonal?). Sections of the hypothalamus showed on microscopic examination aggregations of small cells (germinal centers) in the floor of the third ventricle, also the peculiar vascularization in the tuber cinereum. There were no inflammatory or degenerative changes. The mesenchephalon was normal.

CASE 3.—*History.*—J. G., a boy, aged 3 months, was admitted to the Mount Sinai Hospital on Sept. 15, 1924. He was breast fed for six weeks, and then this feeding was discontinued because of illness of the mother. The child was apparently doing well on a formula until about a week prior to admission, when he began to vomit and to have frequent loose stools (from eight to twelve a day). The stools were watery, green and foul and contained a great deal of mucus.

Examination.—The child appeared acutely ill, rather pale and slightly cyanotic. The skin was dry and cold. The eyes were sunken. Respiration was very rapid. Examination of the blood showed: white cells, 20,500; polymorphonuclear leukocytes, 70 per cent, and lymphocytes, 26 per cent. The urine contained 1 plus albumin but no acetone. The blood sugar was 0.15; the carbon dioxide, 24.

Course.—The child grew steadily worse. Two blood transfusions failed to have any effect, and she died six days after admission. The temperature during observation ranged from 100 to 103 F.

Necropsy Observations.—Thoracic and Abdominal Organs: A portion of the upper lobe of the right lung was atelectatic. The liver showed a few small areas of fatty infiltration. The gastro-intestinal tract and the kidneys were normal.

Brain: The vessels on the surface of the brain were congested, and here and there extravasations of blood into the subarachnoid space were noted. Sections displayed no inflammatory lesions. The grouping of cells in the diencephalon and the characteristic vessel structure in the tuber cinereum were present. The mesencephalon was normal.

CASE 4.—*History.*—A. P., a boy, aged 5 months, was admitted to the Mount Sinai Hospital on Aug. 5, 1929. He was thriving on a formula until two days before admission, when he began to vomit and to have loose watery stools (ten a day).

Examination.—The child was in a state of semi-stupor. He showed marked dehydration; the anterior fontanel was very much depressed. The left ear-drum was somewhat full and red. Examination of the blood showed: hemoglobin, 88 per cent; white cells, 11,000; polymorphonuclear leukocytes, 76 per cent, and lymphocytes, 24 per cent.

Course.—The child was put on a "starvation period," and was given a transfusion and a subcutaneous clysis of dextrose in saline. He seemed to improve; the vomiting ceased, and the diarrhea decreased. Gradually, feedings by mouth were then begun. However, on the sixth day after admission there was a sudden turn in his condition; his temperature rose to 103 F., and he appeared very toxic, though the diarrhea was no longer present and no other cause for the sudden change could be found. The child was given a transfusion by way of the longitudinal sinus. He continued to do poorly and became cyanotic, developed rapid respiration and died on the seventh day after admission. The temperature during observation varied from 99 to 105 F.

Necropsy Observations.—Thoracic and Abdominal Organs: There were bronchopneumonic patches in the upper lobe of the right lung and the lower lobe of the left lung. The liver was slightly enlarged, and the cut surface showed scattered yellowish areas. The gastro-intestinal tract showed areas of congestion throughout the jejunum, ileum and large intestine; some of the lymph follicles of the large intestine were prominent. The kidney showed marked congestion and thrombosis of one of the interlobular veins.

Brain: There was extravasated blood in the subarachnoid space, particularly over the anterior half of the left frontal lobe. Several superficial veins were thrombosed. At the tip of the left frontal lobe there was a thrombosed vein, and the surrounding brain tissue showed some softening. Microscopic examination revealed no inflammatory or degenerative lesions. The typical cell groupings were still in evidence, but they were not as dense or as sharply demarcated as in the previous cases. Some of the cells contained mitotic figures. The vessels were markedly injected, some of them to the point of rupture. It is not unlikely that the subarachnoid bleeding was due to this abnormal distention of the vessels, probably caused by transfusion. The mesencephalon was normal.

CASE 5.—*History.*—J. C., a boy, aged 5 months, was admitted to the Mount Sinai Hospital on July 31, 1929. He had been fed ordinary nonboiled milk. He had been having loose stools for a month. Four days before admission, his temperature rose and he vomited several times.

Examination.—The child was poorly developed and undernourished. He was in a state of stupor and was gasping for breath. The anterior fontanel was markedly depressed. There was a marked loss of tissue turgor. The temperature was 102 F. The hemoglobin was 75 per cent.

Course.—The child was given 150 cc. of citrated blood intravenously. He failed to rally, and died on the second day after admission to the hospital.

Necropsy Observations.—Thoracic and Abdominal Organs: The heart showed a patent foramen ovale. The lower lobes of both lungs showed patches of bronchopneumonia. The thymus was enlarged, weighing 20 Gm. The liver showed diffuse fatty changes. The spleen was congested and showed follicular hyperplasia. The suprarenals showed hemorrhages in the medulla. The gastro-intestinal tract showed no alterations.

Brain: The brain showed subarachnoid extravasation over the dorsal surface of both frontal lobes. On microscopic examination, no abnormal histologic features were noted. The cell groupings and the vascularization of the tuber cinereum were as in normal brains of a corresponding age.

CASE 6.—*History.*—M. H., a girl, aged 7 months, was admitted to the Mount Sinai Hospital on July 25, 1930. Six days prior to admission, the child developed what was taken to be a mild infection of the upper respiratory tract. Four days later she began to have frequent loose stools (six a day) and vomited several times.

Examination.—The child appeared acutely ill. The eyes were sunken and glazed. The cheeks were drawn, and the facial expression was dull. Tissue turgor was poor, and there was marked wrinkling of the skin of the abdomen. There were indefinite signs of a pneumonic process in the left lung. The blood count showed: red cells, 4,650,000; white cells, 13,000; polymorphonuclear leukocytes, 60 per cent, and lymphocytes, 45 per cent.

Course.—Intestinal intoxication was regarded as the most probable diagnosis. The child was given a transfusion of 150 cc. of whole blood and was then given a continuous intravenous drip of 5 per cent dextrose in saline for a period of twenty hours. She responded to this treatment, and the intravenous drip was discontinued. The patient was then given weak tea and subcutaneous injections of dextrose in saline, but she failed to maintain her progress, and was again given a transfusion. After 20 cc. of serum had been administered, the child became cyanotic, and the injection was stopped for a few minutes. As she seemed to recover, the transfusion was resumed; however, after another 20 cc. had been given, she again became cyanotic and died (on the tenth day after admission). The temperature during her stay in the hospital ranged between 98 and 104 F.

Necropsy Observations.—Thoracic and Abdominal Organs: The heart showed parenchymatous degeneration. Both lungs revealed bronchopneumonic infiltrations. The liver was markedly congested, undergoing extensive fatty infiltration, most marked around the central veins. The gastro-intestinal tract was normal, except for scattered areas of congestion as far down as the terminal portion of the ileum. There were found pinhead-sized, elevated, umbilicated areas with punched-out gray centers. Two or three such areas were also found in Peyer's patches. Microscopic study revealed disintegrating villi with a moderate infiltration of polymorphonuclear leukocytes. The oxidase stain showed a large number of polymorphonuclear cells, most numerous in the area of ulceration, but extending in diminishing numbers through the muscularis mucosae with occasional polymorphonuclear cells in the muscular layer. The kidneys showed parenchymatous degeneration.

Brain: The brain showed no gross abnormalities. Microscopic study revealed no inflammatory or degenerative alterations. There was cell grouping in the hypothalamus and subependymal gliosis as in normal brains of similar age. The mesencephalon was normal.

CASE 7.—*History.*—H. R., a boy, aged 9 months, was admitted to the Mount Sinai Hospital on April 22, 1930. For about one week prior to admission the child had had diarrhea and had vomited. The stools increased in number from five to twenty and were green and watery. The temperature had been elevated for the last two days.

Examination.—The child was fairly well developed and nourished. He appeared to be acutely ill. He was restless and irritable. The respirations were deep (Kussmaul breathing). The anterior fontanel was depressed. The abdomen was slightly distended. The tissue turgor over the abdomen was poor. Examination of the blood showed: hemoglobin, 63 per cent; red cells, 4,200,000; white cells, 15,200; polymorphonuclear leukocytes, and 64 per cent, and lymphocytes, 32 per cent.

Course.—The temperature on admission was 101.5 F., and during the next twenty-four hours it rose to 105 F. The child was given a blood transfusion and an intravenous drip of 5 per cent dextrose. She died on the day following admission.

Necropsy Observations.—Thoracic and Abdominal Organs: The heart showed a patent foramen ovale. There were congestion and edema in the lungs. The liver showed infiltration with the fine fat droplets. Peyer's patches of the ileum showed pinpoint ulcerations. Similarly, the solitary follicles of the colon showed ulcerations varying in diameter from pinpoint to 2 mm. Microscopically, Peyer's patches showed degeneration and some infiltration with polymorphonuclears, and the colon showed ulceration over some solitary follicles with necrosis of the adjacent epithelium. The germinal centers of the follicles showed necrosis. The kidneys showed mild tubular degeneration.

Brain: The brain was rather soft and somewhat voluminous; the vessels were congested, with some reddish discoloration of the adjacent cortical areas. On microscopic examination, no inflammatory lesions and no degenerative alterations were found. Cell groupings were less numerous, not as dense and not as well circumscribed as in previous cases. The subependymal gliosis was scanty.

CASE 8.—*History.*—V. H., a girl, aged 9 months, was admitted to the Mount Sinai Hospital on Dec. 11, 1928. During the five days prior to her admission, she had had frequent loose green stools. She vomited once daily. She did not cough, and had no rise in temperature.

Examination.—The child showed marked dehydration. The anterior fontanel was depressed. The eyes were slightly sunken. The abdomen was scaphoid. The tissue turgor was poor.

Course.—A six hour starvation period was instituted, and fluid was given by subcutaneous injections. This was followed by a small amount of 5 per cent dextrose in water by mouth. The patient appeared to be doing well for the first twelve hours. Her breathing then became rapid and deep, the pulse became imperceptible, and the temperature rose to 102 F. Epinephrine, caffeine and 250 cc. of 10 per cent dextrose were administered. The patient rallied for about an hour. Pulmonary edema developed, and she died on the sixth day after admission.

Necropsy Observations.—Thoracic and Abdominal Organs: The lungs were edematous and hyperemic. The liver showed fatty degeneration. The stomach contained a moderate amount of tea-colored fluid chyme. The stomach mucosa was very pale and covered with mucus. The intestines contained a small amount of yellowish-brown liquid. The intestinal mucosa was pale; Peyer's patches were slightly enlarged and hyperemic, and almost all the lymph follicles were hypertrophied. Microscopic examination of the colon showed infiltration of the mucosa with lymphocytes, many plasma cells and occasional polymorphonuclear leukocytes. The submucosa also showed infiltration here and there. The kidneys showed albuminous degeneration of the tubules.

Brain: Some clotted blood was found overlying the dura in the parieto-occipital region. On reflecting the dura, textensive subpial hemorrhages were found over the dorsal surface of both hemispheres. Microscopic examination revealed no abnormal changes. The cell groupings were less discrete. The vessels in the tuber cinereum retained their peculiar structure.

CASE 9.—*History.*—M. R., a girl, aged 1 year, had two admissions to the hospital. Five days before her first admission (Aug. 23, 1929), she began to have loose stools and vomited repeatedly for two days. At the time of admission, the child was 5 months old. She was in a state of semistupor and showed signs of dehydration; the fontanels were depressed, and there was a marked loss of tissue turgor. A diagnosis of alimentary intoxication was made, and the regular routine

of fluid replacement was followed. It led to gradual improvement. Aside from several febrile periods (from 102 to 103 F.), the temperature remained normal. After one month's residence in the hospital, the child was discharged as cured.

The child was well for six months. One week before her second admisison to the hospital (April 20, 1930), coryza and cough developed, with a rise in temperature. For two days before reentering the hospital, she had frequent (from fifteen to twenty) green watery stools, and on the second day of admission she vomited repeatedly after feedings.

Examination.—The child was pale and poorly nourished. The respirations were rapid and shallow. The pulse was rapid and weak. The anterior fontanel was depressed. The eyes were sunken. The tissue turgor was extremely poor. There were impaired resonance and numerous moist râles over the bases of the lungs, both anteriorly and posteriorly. Both drums were full.

Course.—The child died a few hours after admission to the hospital.

Necropsy Observations.—Thoracic and Abdominal Organs: The lung showed confluent bronchopneumonia of all lobes, with acute fibrinous pleuritis. The liver showed marked fatty infiltration. The spleen was enlarged and somewhat flabby. The stomach was dilated to about one and one-half or two times the normal size. The intestinal tract was normal. The mesenteric glands were moderately enlarged. The Kidneys showed marked albuminous and granular degeneration. There was evidence of a bilateral pyelitis. The suprarenals showed some hemorrhage in the medulla. Both middle ears contained a moderate amount of thin, grayish pus.

Brain: The brain showed congestion of the pial vessels. Microscopic examination disclosed fairly marked subependymal gliosis, but not outside of normal variations. Cell groupings were less marked, but still present, particularly along the developing tracts, where the cells were oriented in a longitudinal plane. The mesencephalon was normal.

COMMENT ON ANATOMIC OBSERVATIONS IN INTESTINAL INTOXICATION

The material for this study was assembled after a thorough and critical survey of the clinical manifestations and the necropsy observations in selected cases. Questionable cases were eliminated, and, as a result, only nine of a larger number of available cases of intestinal intoxication are herein reported. In every one of the nine cases so chosen, the more important signs and symptoms typifying this disease were present. There were the onset with frequent loose stools, vomiting and rapid dehydration, and the intense toxicity; and restlessness or semi-stupor, Kussmaul breathing, feeble pulse and elevated temperature were among the constant manifestations. Sudden collapse preceded the fatal issue. Moderate variations were present in individual cases, only one or more of the features described by Finkelstein [9] occasionally being absent.

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9. Finkelstein, H.: Ueber alimentäre Intoxication im Säugligsalter, Berlin, S. Karger, 1910.

Some of the cases have shown evidence of focal infections, such as otitis media (case 2) or infection of the upper respiratory tract (cases 6 and 9). These changes do not cloud the diagnosis, as it is realized that the coexistence of such focal infections is not uncommon in intestinal intoxication as a complication or a terminal event.[10]

From the general necropsy reports, we gather little information as to the etiology of the disease, nor important data that would question the clinical diagnosis made in the nine cases. The few changes in the intestinal tract, exfoliation, follicular hyperplasia, etc., and the mild leukocytic invasion cannot be regarded as pathognomonic of the disease. They are frequently found when death occurs as the result of some other disease, and, again, they were found only in three of our nine cases (cases 6, 7 and 8). They are certainly not sufficient to explain the profound intestinal disorder. While it is generally assumed that the gastro-intestinal tract is essentially normal in cases of alimentary intoxication, occasional lesions are reported.[11]

In four of our cases (cases 1, 4, 5 and 6) pneumonic processes were found, which were most likely terminal rather than precipitating events. To detect any pathologic alterations in the brain, a thorough search, which included a survey of a large number of histologic preparations (approximately 2,000), taken from various parts of the brain, was made, and it failed to reveal any evidence of an active inflammatory or toxic degenerative process in the brain of infants who had died in the course of intestinal intoxication. Occasional petechial hemorrhages and frequent microscopic subarachnoid bleeding were noted, but they, we have reason to assume, played no important rôle in the clinical picture and were but terminal events, which, in several instances, we believe were due to massive infusion of fluids into a weakened vascular system. In this study, we have investigated with particular care the region about the third ventricle and have found there circumscribed collections of deeply staining cells, which are constantly noted in normal brains and are often mistaken for inflammatory lesions.

Schob [4] called attention to these cell groups in the following words:

> Many cell islands and cell groups often remain up to the first few months after birth or even longer between the nerve bundles in the inbetween layers to be finally transformed into glia. These groups of cells are most often in the vicinity

10. Wishart, D. E. S.: Relations of Infection of the Ear and Infections of the Intestinal Tract in Infants, J. A. M. A. **95**:1084 (Oct. 11) 1930. Brown, A.; Tisdall, F. F.; Wishart, T. G. H., and Johnston, M. M.: Etiology of Acute Intestinal Intoxication of Infants; Preliminary Report, South. M. J. **23**:107 (Feb.) 1930.

11. Adam, A., and Froboese, C.: Untersuchungen zur Pathologie der Durch-Fallerkrankungen des Säuglings, Ztschr. f. Kinderh. **39**:267, 1925.

of the ventricles. They may be free or situated at the bifurcation of blood vessels or forming a half moon around the vessels. Very often they may just be cellular extensions from the matrix, then their origin is better understood.

. . . There is a difference of opinion as to the abnormality of finding germinal centers (Keimbezirke) in the brain of the new-born. These centers have been incorrectly interpreted even by renowned authors. They have been considered as lymphocytic infiltrations or as accumulations of glia cells following proliferative inflammatory processes and have been used to support the theory of the inflammatory character of changes found in such brains. Thus, it has been used as proof of the encephalitic origin of the so-called encephalitis congenita of Virchow.

In the light of the foregoing view, supported by Spielmeyer as well as by our own observations, it may now be said emphatically that such cellular accumulations, when found particularly in paraventricular zones of the brain of an infant, are but the normal expression of the histogenetic process. It is obvious that similar cellular aggregations in the hypothalamus, when found in intestinal intoxication, must not be regarded as bearing any relation to the clinical features of the disease, and obviously play no rôle in the production of the disease. To this may be added that since no inflammatory or degenerative changes were found in the brains of infants dying of intestinal intoxication, it may be concluded that in our material, consisting of nine cases of intestinal intoxication, there was no evidence of an encephalitic process, and no data to support the assumption of Goldzieher that such a process is responsible for the clinical manifestations in this disease. His term diencephalitis dehydrans is therefore not warranted by facts.

SUMMARY AND CONCLUSIONS

1. Some well established, but not widely known, anatomic features characterizing certain stages in the developing brain are described.

2. They often assume the form of circumscribed collections of deeply staining cells, which are often erroneously considered of inflammatory origin.

3. Nine cases of intestinal intoxication are described. They revealed no evidence of an inflammatory or degenerative disease in the brain.

4. Evidence is presented against a recent view that an encephalitic process in the diencephalon, affecting certain hypothalamic centers, causes the dehydration of intestinal intoxication.

5. The conclusion is reached that no pathologic alterations were found in the brains studied to account for the clinical picture in intestinal intoxication.

Case Reports

CIRRHOSIS OF THE LIVER IN CHILDREN*

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Cirrhosis of the liver in childhood is sufficiently rare, at least in America, to justify us in adding a report of our case to the literature. This case is reported in particular because it involves the differential diagnosis of a number of specific cirrhoses of the liver usually grouped under the loose and misleading term of hypertrophic cirrhosis, each, however, having a different prognosis and demanding a somewhat different therapy. The case herein reported is the second case on record in the English literature in which the patient was treated by surgical drainage.

REPORT OF A CASE

History.—C. G., a white boy, 11 years of age, was admitted to Cook County Children's Hospital on Sept. 23, 1930, with the complaints of jaundice and abdominal distention. The mother stated that the child seemed well until Nov. 1, 1929 (eleven months before admission), when jaundice was first noted. The jaundice continued and became progressively worse until January, 1930, when it diminished; the following month, however, it again deepened. The jaundice persisted until the time of admission, with periods of greater and lesser intensity. During the periods when the jaundice was most marked, the boy occasionally complained of feeling feverish. Shortly after the onset of the jaundice, abdominal distention was noted. This condition persisted and became progressively more marked. Occasionally pain in the upper right quadrant of the abdomen was complained of, particularly when the jaundice was most marked. Vomiting occurred only once. The mother stated that one week before admission the boy expectorated a wineglassful of thick, dark blood. She said that the stools were not clay-colored and were usually yellow; the urine was described as "yellowish staining."

The child's past history was essentially unimportant, except for the significant fact that in 1927 there was an attack of jaundice accompanying a gastro-intestinal upset, which lasted for two weeks and then cleared up completely. No history of alcoholism or family history of jaundice could be obtained. Four older children in the family were living and well. No history of cirrhosis of the liver in any other member of the family could be obtained.

Examination.—Examination revealed a normally developed but somewhat undernourished white boy, 11 years of age, with a moderate generalized icterus, who did

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* From the Pediatric Department of the Cook County Hospital. Presented before the Chicago Pediatric Society, March 19, 1931.

not appear acutely ill. The temperature was 99 F.; the pulse rate, 100, and the respiratory rate, 20. The sclerae showed moderate icterus, but no wedge-shaped yellowish areas were seen in the conjunctiva. The lips showed a few small herpetic lesions. Palatal icterus was present. The neck, heart and lungs were normal. The abdomen was markedly enlarged. The liver was much enlarged, the right lobe extending 2 inches (5 cm.) below the transumbilical line (fig. 1). The liver felt hard and smooth and was not tender. The spleen was enlarged two fingerbreadths below the costal margin. There was no demonstrable ascites or edema of any part of the body.

The impression at this time was that the case was one of Hanot's cirrhosis, because this type occurs in young persons, especially males, without a history of alcoholism, and because of the presence of moderate jaundice without definite obstruction, the markedly enlarged, smooth painless liver, the enlarged spleen and the absence of ascites. The history also revealed periodic attacks of fever, increased intensity of jaundice and abdominal pain. Clubbing of the fingers was also present.

Preoperative Laboratory Examination.—The blood counts are given in table 1. Blood smears showed young polymorphonuclear cells, a tendency toward increased

TABLE 1.—*Blood Counts Made Before Operation*

Date	Red Blood Cells	Hemoglobin	White Blood Cells	Polymorphonuclears	Lymphocytes	Large Mononuclears	Eosinophils	Basophils
Sept. 24	.....	....	11,700	55	43	2	..	..
Sept. 27	3,500,000	65%	12,200	60	35	4	1	..
Oct. 13	3,360,000	64% 10.9 Gm. (Newcomer)	6,450	65	25	9	1	..
One month after operation	3,800,000	70%	7,200	65	26	8	..	1

diameter of the red blood cells, slight anisocytosis and no microcytes; the blood platelets were large and appeared plentiful. There were 1.5 per cent of reticulocytes. The platelet count was 180,000 (Fonio's method). The bleeding time was four minutes, and the coagulation time was eight minutes. The fragility test (hematocrit method) showed increased resistance or decreased fragility. Bilirubin measurement showed 4.6 units or 2.3 mg. per hundred cubic centimeters of blood (the normal value is from 0.5 to 1.0 unit and from 0.25 to 0.5 mg. per hundred cubic centimeters). The Wassermann and Kahn reactions of the blood were negative.

Routine urinalysis showed bile and urobilinogen. The stools varied; some specimens showed moderate amounts of bile, and others none. Cultures of stools gave negative results.

The Pirquet and Mantoux tests were negative. The agglutination test of the blood was negative for Bacillus typhosus and B. paratyphosus B, but positive for B. paratyphosus A through a dilution of 1:320, and partial for 1:640. Urea nitrogen was 17, and cholesterol, 178 mg. per hundred cubic centimeters.

A roentgenogram of the chest was negative. The Graham-Cole test showed nonvisualization of the gallbladder.

Course.—During the four weeks following admission to the hospital, the temperature varied between 98 and 100 F. and occasionally went as high as 101 F. One week after admission, a therapeutic test with mercury rubs and potassium iodide was made. Throughout this period of three weeks of antisyphilitic therapy,

there was no improvement in the general condition, the jaundice or the size of the liver, and an exploratory laparotomy with drainage through the gallbladder was decided on.

Operation.—An exploratory laparotomy was done on Oct. 21, 1930 (four weeks after admission), by Dr. E. Miller. The liver was enlarged to below the umbilicus. It was firm and smooth, and the surface was yellow-green. The spleen was smooth and enlarged about two fingerbreadths below the costal margin. A splenic puncture was made. The gallbladder was pale and flabby and contained no stones. Careful

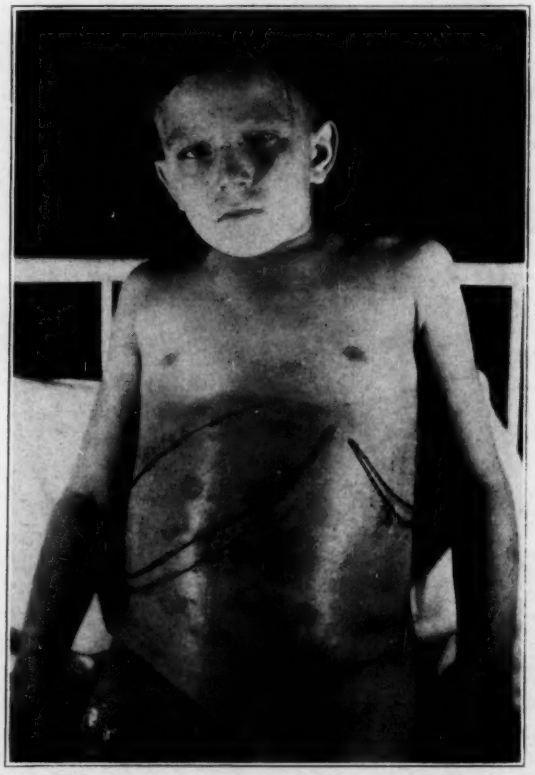

Fig. 1.—Photograph taken five weeks after operation (Nov. 24, 1930). The lowest penciled line outlines the lower border of the liver before operation. The middle line outlines the lower border of the liver five weeks after operation; the upper line, the costal margin; the penciled lines on the left, the palpable portion of spleen. The abdomen was still considerably distended.

examination showed no obstruction of the larger bile ducts. The gallbladder was opened, and the contents consisted of yellow, stringy bile; no fluid bile was present. The material was transferred to various culture mediums. A small piece of liver was also removed from the left lobe for microscopic study. A rubber tube was inserted into the gallbladder for drainage.

Postoperative Course.—The patient made an uneventful recovery from the operation. There was no drainage during the first twenty-four hours; on the

following day, however, there was a profuse greenish-yellow, odorless, semiliquid drainage. The profuse drainage continued for a week and then gradually lessened. The drain was removed on November 11 (three weeks after operation), at which time there was still a slight amount of mucoid discharge. During the first and second postoperative day, the temperature ranged between 98 and 102 F. Throughout the remainder of the patient's stay in the hospital, the temperature was normal.

Laboratory Findings After Operation.—Smears of splenic puncture made at the time of operation were negative for any pathologic evidence. The differential count was: polymorphonuclears, 53 per cent; lymphocytes, 36 per cent; monocytes, 9 per cent; eosinophils, 1 per cent and irritation forms, 1 per cent.

Cultures of the bile obtained at the time of operation were negative.

Fig. 2.—Photograph taken four and a half months after operation (March 3, 1931). The penciled lines outline the palpable portion of liver below the costal margin. The liver has receded from below the umbilicus before operation to midway between the umbilicus and the costal margin. The abdomen was slightly distended; the spleen was not palpable.

Routine examinations of the urine made after operation were negative for bile and urobilinogen.

Examinations of the stool following operation showed bile.

On November 15 (three and one-half weeks after operation), the icterus index was 12 (but probably normal owing to the presence of a slight hemolysis). The van den Bergh test (indirect) made on the same day gave normal results, and there was not sufficient bile in the blood at this time for a quantitative bilirubin test (compared to a bilirubin of 4.6 units before operation).

Blood agglutination tests made on November 18, were negative for typhoid, B. paratyphosus A and B, Hiss Y and Shiga and Flexner organisms.

Course after Discharge from Hospital.—The child was allowed to leave the hospital on November 18. At this time, there was a notable lessening of the icterus, and he weighed 68 pounds (30,800 Gm.), compared to 63 pounds (28,600 Gm.) on entrance.

The patient was again seen in December, 1930. At this time, the liver was appreciably smaller, extending only to the transumbilical line.

On March 3, the child weighed 85 pounds (38,600 Gm., a gain of 17 pounds (7,700 Gm.) since leaving the hospital. The abdomen was much less distended (the parents noticed that the boy's vest was loose). The liver extended midway between the costal margin and the umbilicus (fig. 2). The spleen was not palpable. The jaundice was practically absent.

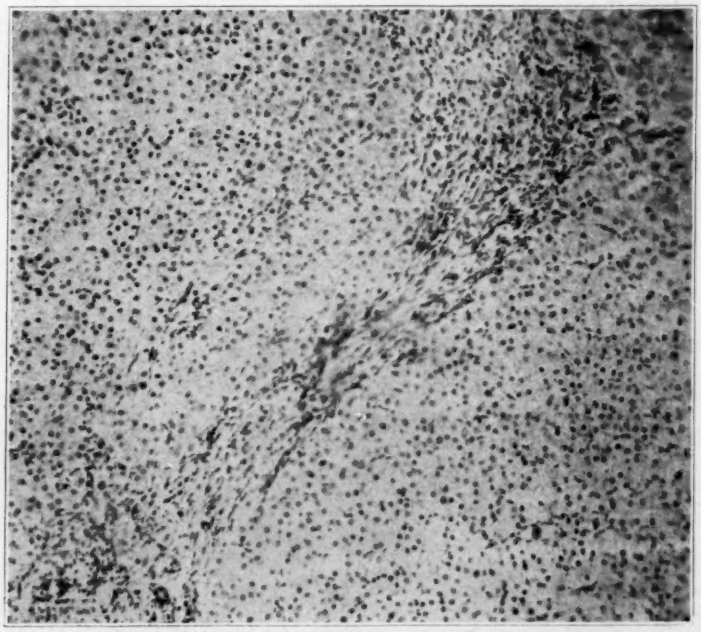

Fig. 3.—Fibrosis with a large strand of fibrous tissue running from one periportal area to another and separating the two lobules of the liver; infiltration of fibrotic tissue with lymphocytes, especially adjacent to the periportal spaces. Degeneration of the liver cells occurs only adjacent to the fibrosis, and is especially marked adjacent to the periportal spaces. There is moderate infiltration of fibroblasts and lymphocytes between strands of liver cells adjacent to the periportal spaces.

At the time of writing (June 15), the liver was barely two fingerbreadths below the costal margin. A slight icterus of the conjunctiva was still present. The patient weighed 90 pounds (40,820 Gm.) ate well, looked well and attended school regularly.

Pathologic Report.—(Dr. R. Jaffe and Dr. Otto Saphir aided in interpreting the microscopic observations.)

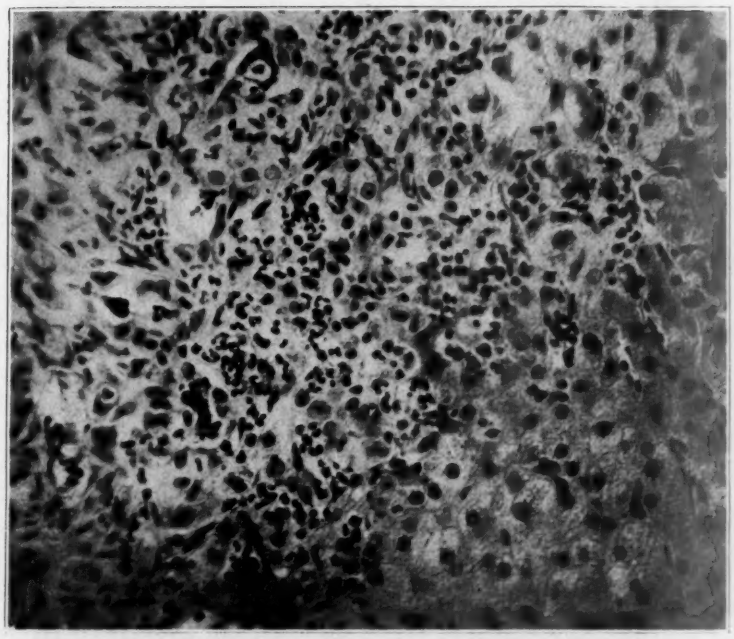

Fig. 4.—Accumulation of large numbers of polymorphonuclear leukocytes and endothelial leukocytes in the periportal area, especially in the smaller bile ducts, distending and filling them. Adjacent liver cells are large with granular cytoplasm, which indicates degeneration.

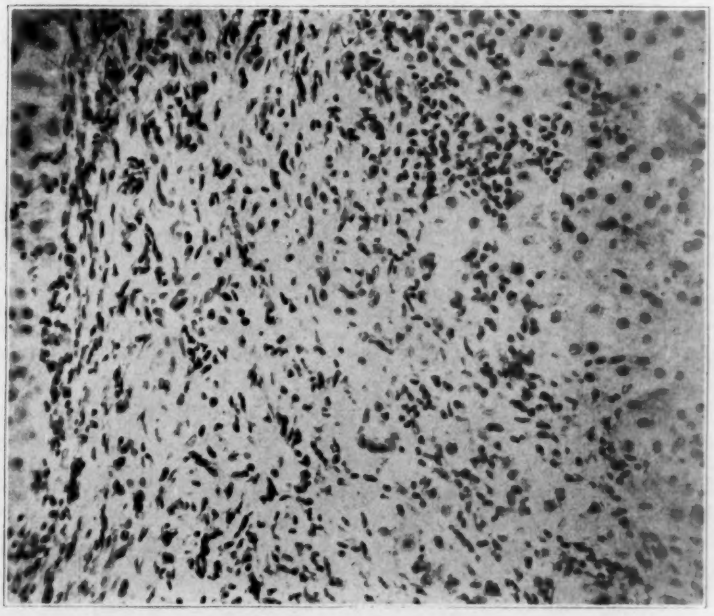

Fig. 5.—The periportal space in which are many newly formed bile ducts, lymphocytic infiltration and many fibroblasts.

The picture varied in the different fields of the liver examined, as the inflammatory reaction was not equally advanced in all the portal areas. Some fields showed acute, others chronic and others, healing reactions. The lesions were confined to the portal and periportal areas and the adjacent liver cells; that is, about the periphery of the lobules where the process was active. The small terminal bile ducts were the center of an acute inflammatory reaction. The lumen was distended with polymorphonuclears and endothelial leukocytes. The surrounding stroma was also infiltrated with an acute inflammatory exudate. Proliferation of fibroblasts occurred even in the early stages. In some of the older areas of healing, infiltration with lymphocytes and proliferation of fibroblasts were the most prominent features. As the process extended, adjacent liver cells in the outer portion of the lobule degenerated. The bile duct epithelium proliferated, the ducts were dilated and the small bile ducts appeared increased in number and extended

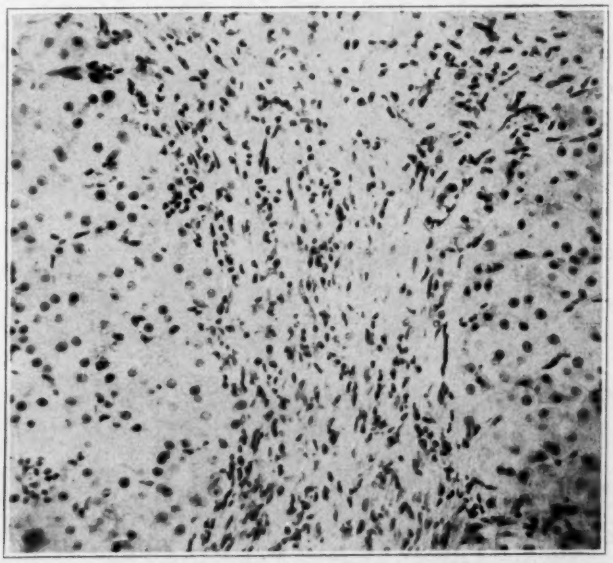

Fig. 6.—Marked periportal fibrosis, lymphocytic infiltration and adjacent degeneration of liver cells. In stained sections, a moderate amount of bile pigment is seen deposited in region of periportal spaces.

into the zone of necrosis. The true lobular arrangement was preserved, and the portal areas showed up as broad bands of connective tissue running regularly between the lobules of liver cells. There was rarely any cutting into a lobule by large strands of connective tissue. Inspissated deposits of bile pigments were found in the periportal areas due to the inflammatory exudate which obstructed some of the smaller bile ducts.

The increase in the size of the liver was the result of the extensive inflammatory exudation and the regeneration of the connective tissue. It was smooth, owing to the even distribution of the inflammatory process. The inflammatory exudation in the smaller bile ducts caused some obstruction to the outflow of bile, resulting in a moderate clinical jaundice. No ascites or obstruction to the portal blood flow was present. In figures 3, 4, 5 and 6 are shown sections of liver tissue.

REVIEW OF THE LITERATURE

In a recent review of the American literature on cirrhosis of the liver, Sutton [1] reported twenty-three cases in which he considered the diagnosis was atrophic cirrhosis. In approximately sixteen of them the livers were considerably enlarged. He apparently called all the cases of Laennec's or portal cirrhosis, whether alcoholic or not, atrophic, even though the livers may have been in the hypertrophic stage of portal cirrhosis. In our own review, we have included all cases of cirrhosis reported in the American literature in which appreciable enlargement of the liver was shown clinically or pathologically, because such cases represent at least the hypertrophic stages of the cirrhotic livers.

Thirty-six reported cases of cirrhosis, accompanied by considerable enlargement of the liver in childhood, are tabulated. This tabulation has been somewhat difficult and confusing. Many of the reports of cases contain no autopsy report and, consequently, no microscopic study of the liver sections. An exact diagnosis of the type of cirrhosis can be made only on microscopic study of liver tissue, and so in some of the reported cases, the accuracy of the diagnosis is open to question. Some of the tabulated cases have been included under the heading "hypertrophic cirrhosis" merely on the basis of the presence of a large liver.

A brief summary of the tabulation follows: Eighteen patients were male and fourteen, female. The sex was not stated in four cases. Seven patients gave a history of alcoholism. Syphilis was suspected in three cases and proved in another. Twenty-five patients had jaundice; five did not have it, and in six cases, jaundice was not mentioned. Ascites was present in fifteen cases, absent in twelve, and not mentioned in nine. All of the patients had large livers. The spleen was enlarged in twenty-one cases; it was not enlarged in four cases, and the size was not stated in eleven cases.

Of the thirty-six cases, autopsy was performed in only seventeen. Seven could be classified microscopically as Laennec's cirrhosis or as portal cirrhosis in the hypertrophic or large liver stage and two as infectious cirrhosis. Most of the remainder were merely described as "hypertrophic" cirrhosis, a vague term.

Apparently in children the cirrhotic liver is frequently found in the hypertrophic stage; whereas, in adults it is most always in the atrophic stage. This may be due to the fact that the condition runs a more acute course in children; perhaps death occurs before the atrophic changes can take place.

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1. Sutton, T. L.: Cirrhosis of the Liver in Childhood, Am. J. Dis. Child. **39**:141 (Jan.) 1930.

TABLE 2.—*Cases of Cirrhosis in Children Presenting Large Livers (American Literature)*

No.	Age	Sex	Alcohol	Syphilis	Icterus	Ascites	Spleen	Liver	Author
1	4 mos.	Not stated	Not stated	Not stated	Progressive	Moderate	Enlarged	Liver section characteristic of subacute cirrhosis	Oertel (Canad. M. A. J. **6**: 472, 1916)
2	6 mos.	M	No	Not stated	Present	Not stated	Enlarged	Enlarged	Tarr (M. J. & Rec. **126**: 293, 1927)
3	9 mos.	F	Not stated	Not stated	No	Not stated	Enlarged	Liver section (at autopsy) showed hypertrophic cirrhosis	Tarr
4	9 mos.	Not stated	Not stated	Suspected	Marked	Marked	Not stated	At one time during life, liver was enlarged but post mortem was smaller than normal; microscopic sections suggested hypertrophic cirrhosis	Hand (Tr. Path. Soc. Philadelphia **18**: 66, 1898)
5	1 yr.	F	Not stated	No evidence; Wassermann test negative	Present	No	Enlarged	Autopsy at 3 years of age; liver several times larger than normal; sections showed the characteristic changes seen in hyptertrophic biliary cirrhosis	Tarr
6	14 mos.	M	Not stated	Not stated	Present	Not stated	Enlarged	Liver enlarged	Tarr
7	14 mos.	F	No	No evidence; Wassermann test negative	Present	Appeared two weeks before death	Enlarged	Cirrhosis was monolobular in type, with a great proliferation of the bile ducts, many of which were irregularly formed and surrounded by an abundance of young fibrous tissue	Day (Canad. M. A. J. **15**: 370, 1925)
8	16 mos.	F	Yes	No evidence	No	Marked	Enlarged	Liver, smooth and hard, extending down almost to the spine of the ileum	Abrahams (Pediatrics **9**: 186, 1900)
9	2 yrs.	F	Not stated	No evidence; Wassermann test negative	Persistent and generalized	No	Enlarged	Liver 5 inches (2.3 cm.) below costal margin; smooth edge	Abt (M. Clin. North America **3**: 13, 1919)
10	2 yrs.	F	Not stated	No evidence; Wassermann test negative	No	No	Enlarged	Enlarged; histologic examination of liver section (at autopsy) showed hypertrophic stage of portal cirrhosis	Reuben and Peskin (Arch. Pediat. **47**: 715, 1930)
11	2½ yrs.	M	No	Not stated	Marked	Present	Not stated	Liver enlarged and hard (no autopsy)	Marsh (M. Rec. **27**: 684, 1885)
12	3 yrs.	M	Not stated	Not stated	Present	Not stated	Not stated	Liver from two to three times normal size and much increased in consistence; surface and cut section smooth; bacteria found in microscopic sections	Mallory (Bull. Johns Hopkins Hosp. **22**: 69, 1911)
13	3½ yrs.	F	Yes	Excluded; Wassermann test negative	Not stated	No	Not enlarged	Enormously enlarged	Elterich (Atlantic M. J. **30**: 788, 1927)
14	4 yrs.	M	Yes	Wassermann test negative	Marked	Terminal	Enlarged	Clinically, enlarged 5 cm. below costal margin; at autopsy, liver large, firm and nodular; reported as atrophic cirrhosis with regeneration	Ely (Boston M. & S. J. **170**: 542, 1914)
15	4 yrs.	M	Yes	No evidence	Marked	No	Enlarged	Liver palpable 7 cm. below costal margin; liver edge smooth and firm; no autopsy	Ely
16	4½ yrs.	M	Yes	No evidence	Not present	No	Not enlarged	Liver enlarged down to the level of the umbilicus; surface felt even and smooth; no autopsy	Blakely (Boston M. & S. J. **162**: 245, 1910)
17	6 yrs.	..	.....	.....	.....	.....	.....	Called a case of hypertrophic cirrhosis in textbook	Griffith and Mitchell (Diseases of Infants and Children, Philadelphia, W. B. Saunders Company, 1910, vol. 2, p. 221)

17	6 yrs.	..	.....	.....	.....	.....	.....	Called a case of hypertrophic cirrhosis in textbook	Griffith and Mitchell (Diseases of Infants and Children, Philadelphia, W. B. Saunders Company, 1910, vol. 2, p. 221)
18	6 yrs.	F	No	Excluded	Mild	No	Not stated	Liver large, smooth, hard and painless, extending down to navel	Fotheringham (Canada Pract. & Rev. **27**: 885, 1902)
19	7 yrs.	Not stated	Not stated	No evidence	Not stated	No	Enlarged	Abdomen enlarged; superficial veins distended; liver edge felt just below navel—smooth	Osler (Bull. Johns Hopkins Hosp. **14**: 322, 1903)
20	7 yrs.	M	Not stated	No evidence	Slight	Not stated	Not stated	Liver enlarged; no autopsy	Bringier (Philadelphia M. J. **5**: 1210, 1900)
21	8 yrs.	F	Not stated	Wassermann test positive	Present	Terminal	Enlarged	Liver enlarged; reported as syphilitic cirrhosis because of positive Wassermann test	Reuben and Peskin
22	8 yrs.	M	No	Negative history	Variable	Present	Not enlarged	When patient was first observed, liver extended to umbilical line; at time of death (18 months later) liver was palpable 2 cm. below costal margin; no autopsy	Hamilton (Internat. Clin. **2**: 244, 1903)
23	8 yrs.	M	Not stated	Suspected but not proved	Not stated	No	Not stated	Enormously enlarged and characteristically hobnail (at autopsy)	Forchheimer (Tr. A. Am. Physicians **2**: 1, 1887)
24	9 yrs.	F	Tastes of cordial	Negative history	Intermittent	Present	Not stated	Liver enlarged down to umbilicus	Hollopeter (M. News **80**: 253, 1902)
25	9 yrs.	F	No	No	Yes	Yes	Enlarged	Enlarged, granular, tough, anemic, dirty white, termed hypertrophic	Howard (Tr. A. Am. Physicians **2**: 1, 1887)
26	10 yrs.	M	No	Not stated	Present	Present	Enlarged	Enlarged microscopically, active interstitial change; hyperplasia of interlobular connective tissue and hyperplasia of newly formed bile ducts	Freeman (Arch. Pediat. **17**: 81, 1900)
27	10 yrs.	F	No	Not stated	Present	Variable	Enlarged	Enlarged	Jacobi (Arch. Pediat. **6**: 273, 1889)
28	10 yrs.	M	No	No	Yes	Yes	Enlarged	Enlarged	Howard
29	10 yrs.	M	No	No evidence	Slight	.....	Enlarged	Greately enlarged (same case later reported by the same author as case of atrophic cirrhosis)	Edwards (Arch. Pediat. **7**: 502, 1890; **12**: 481, 1895)
30	11 yrs.	M	Yes	Excluded	Absent	Marked	Not enlarged	Liver extended three fingerbreadths below the costal margin; the edge was irregular and the surface felt rough and hard; no autopsy	Kay (J. Michigan M. Soc. **21**: 244, 1922)
31	12 yrs.	F	No	Excluded	Not stated	Marked	Not stated	Liver enlarged	Fotheringham
32	12 yrs.	F	Not stated	Not stated	Present	Not stated	Not stated	Liver three times normal size; surface and cut section smooth; bacteria found in microscopic sections	Mallory
33	13 yrs.	M	Not stated	No evidence	Deep	No	Enlarged	Liver down three and one half fingerbreadths; smooth and hard	Abt (Pediatrics **13**: 404, 1902)
34	13 yrs.	M	Yes	No evidence	Not present	No	Enlarged	At autopsy liver found considerably enlarged; surface hobnailed; microscopic examination showed the ordinary changes found in cirrhosis	Biggs (M. Rec. **38**: 206, 1890)
35	13 yrs.	M	Not stated	Negative history	Present	.....	.....	Family told child had hypertrophic cirrhosis (case not seen by author)	Bamberger (J. A. M. A. **75**: 743 [Sept. 11] 1920)
36	16 yrs.	M	Not stated	No evidence	Marked	No	Enlarged	(Patients in cases 35 and 36 were brothers); at autopsy, liver was large, greenish-yellow on surface; sections showed hypertrophic cirrhosis	Bamberger

COMMENT

In this discussion, we are mainly concerned with the large liver type of cirrhosis. The classification of cases in which the patients present enlarged cirrhotic livers often associated with jaundice presents difficulties to the clinician. This particularly pertains to certain types of cases greatly resembling the classic syndrome of Hanot's [2] cirrhosis, such as the reported case, but in which microscopic examination does not reveal the essential pathologic changes of Hanot's cirrhosis. Most of the children with the large liver type of cirrhosis whose cases have been reported in the literature had symptoms and physical signs similar to those present in our case; these are generally mentioned in the textbooks as symptoms of Hanot's cirrhosis. The patient is youthful, often a male, with a marked chronic, relatively painless enlargement of the liver, which is smooth, hard and not tender, and with enlargement of the spleen and moderate jaundice which fluctuates in intensity. The jaundice is usually most marked during febrile periods and is accompanied by leukocytosis and abdominal pain. Ascites is usually absent as in our case, but it has been present in some of the reported cases. There was no history of alcoholism in our patient. This type of condition is commonly spoken or written of as hypertrophic cirrhosis or hypertrophic biliary cirrhosis. These terms are very loose and poor, because a number of conditions of different etiology, prognosis and therapy are included in them; namely, infectious cirrhosis, obstructive cirrhosis, certain forms of congenital syphilitic cirrhosis, Hanot's cirrhosis, the hypertrophic stages of Laennec's cirrhosis or portal cirrhosis, and Banti's disease. Clinically, it is often difficult to differentiate these forms; consequently, if the patient fails to respond to antisyphilitic treatment, an exploratory laparotomy with the removal of a small section of liver tissue for microscopic study may be justifiable, as in our case.

Regarding the use of the terms "hypertophic" and "atrophic," many pathologists feel that such terms should be abandoned, as they do not designate the disease entity clinically or pathologically.

According to Mallory,[3] the term "cirrhosis of the liver," in the broadest sense, is applied to all sclerosed conditions of the liver, whether progressive or not, in which destruction of liver cells is associated with real or apparent increase of connective tissue. The terms "hypertrophic" and "atrophic" cause much confusion. A large hypertrophied, smooth liver may occur in at least six different types of cir-

2. Hanot: Thèse de Paris, 1875. Lereboullet, P.: Les cirrhoses biliares, Paris, Masson et Cie, 1902.

3. Mallory, F. B.: Bull. Johns Hopkins Hosp. **22**:69, 1911; Hemochromatosis and Chronic Poisoning with Copper, Arch. Int. Med. **37**:336 (March) 1926.

rhosis: alcoholic, infectious, pigmentary, Hanot's, syphilitic and obstructive. If acute necrosis of liver cells and exudation cease and healing occurs, or if the process is of low grade and long duration so that healing and scar tissue are more prominent than degeneration and exudation, the liver will become smaller. Atrophic cirrhosis is simply a condition in which a large proportion of the liver cells have been destroyed, while the existing and new connective tissue has become prominent. This may occur in at least three different types of cirrhosis: toxic (central necrosis), syphilitic and Laennec's (alcoholic). Consequently, according to Mallory, it is best to discard the terms "atrophic" and "hypertrophic," or at least to reserve them as descriptive of the stage of cirrhosis rather than the kind.

DIFFERENTIAL DIAGNOSIS

The essential differential features that distinguish the various types of so-called hypertrophic cirrhosis, as shown by examination of sections microscopically, are as follows:

Infectious Cirrhosis.—The pathologic changes are confined almost entirely to the region around the portal vessels and adjacent areas, spreading out from the small terminal bile ducts which are dilated and some of which are filled with polymorphonuclear leukocytes. The liver cells adjacent to the periportal areas about the periphery of the lobule are necrotic. Proliferation of fibroblasts with much increase of connective tissue occurs in the portal and periportal areas, which are also infiltrated with leukocytes and later with lymphocytes. The portal tissues show up as broad bands of connective tissue running regularly between the lobules of liver cells, preserving the true lobular arrangements. Clinically, the findings are similar to those described in our case.

Laennec's (Alcoholic or Portal) Cirrhosis; Hypertrophic Stage.—Degeneration of groups of liver cells situated in any part of the lobule occurs with regeneration of adjoining liver tissue. Connective tissue replaces the necrotic liver cells. As the degeneration and replacement may have any distribution in the lobule, the broad bands of connective tissue cut into the lobules in every direction, distorting the lobular arrangement in a most disorderly fashion, separating the liver cells into patches or islands of liver parenchyma, without any regular relation to the bile ducts, portal spaces or hepatic veins. Obstruction to the blood flow then occurs, with portal stasis and ascites. Clinically, the presence of jaundice, the absence of ascites and other signs of portal obstruction, and the presence of an enlarged spleen were indications against the diagnosis of Laennec's cirrhosis in the case reported.

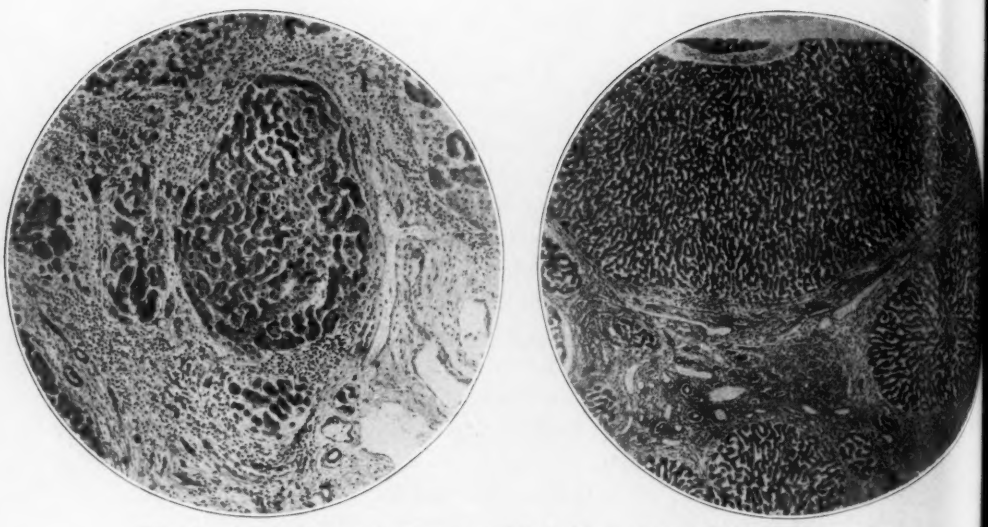

Fig. 7.—Laennec's, alcoholic or portal cirrhosis (from MacCallum's "Pathology"). Islands of liver cells surrounded by dense strands of connective tissue distort the lobular arrangement in a disorderly fashion.

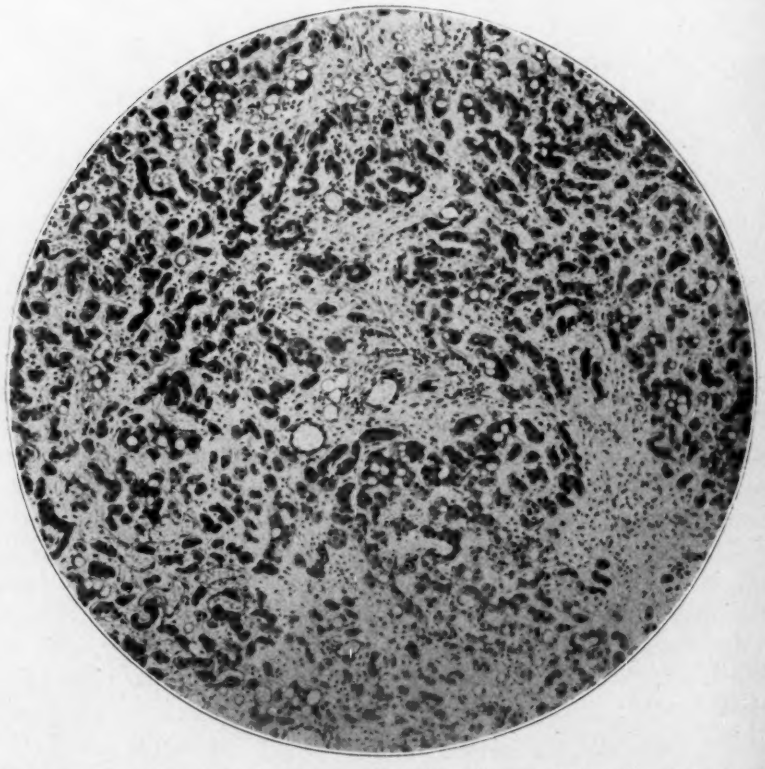

Fig. 8.—Hanot's cirrhosis (from MacCallum's "Pathology") showing the spider-web-like intralobular and intercellular fibrosis.

Hanot's Cirrhosis.—Connective tissue penetrates the lobules as a fine network between the cell columns, separating them into almost isolated single cells and giving a spider-web appearance to the liver lobule. This intralobular and intercellular connective tissue retains its nuclei for a long time and does not contract. The compressed liver cells tend to atrophy. The connective tissue may also appear between the lobules as broader strands. Clinically, the symptoms strikingly resemble those of our case (infectious cirrhosis).

Syphilitic Cirrhosis.—In syphilitic cirrhosis, especially the congenital type in which a diffuse lesion predominates, the presence of gummas, endarteritis and spirochetes are the outstanding differential features. Clinically, the absence of other signs of syphilis, the lack of response to syphilitic therapy and the negative reactions of the Wassermann and Kahn tests were indications against a syphilitic liver in the case reported.

Obstructive Cirrhosis.—Obstructive cirrhosis rarely occurs alone; sooner or later it is usually complicated by infectious cirrhosis. Obstructive cirrhosis results from prolonged biliary obstruction, and the observations somewhat resemble those of infectious cirrhosis, except that in the obstructive type there is a much more uniform distribution of the cirrhosis throughout the liver. There is also extreme bile stasis not seen in the purely infectious type, with resulting inflammatory and degenerative changes. In the purely obstructive type, the liver is not as markedly enlarged and there is never portal obstruction. Clinical or surgical evidence of the obstruction (that is, stone in the common duct) confirms the diagnosis. Obstructive cirrhosis, at least in the early stages, is much more common as a pure type than infectious cirrhosis. Most of the cases of infectious cirrhosis have been superimposed on an obstructive cirrhosis.

Although this is rare, infectious cirrhosis can exist as a pure type without obstruction, as in the case herein reported. (Careful surgical exploration revealed no evidence of obstruction in the larger bile ducts.)

Other Conditions.—A type of cirrhosis of the liver seen only in certain parts of India should be mentioned. This is called "infantile biliary cirrhosis" and has a definite hereditary tendency and familial incidence. It is highly fatal. For a more detailed discussion, Mukherji [4] and Iyer [5] may be consulted.

Other conditions that were considered in the clinical preoperative differential diagnosis were the following: a primary or secondary malignant disease of the liver, ruled out because the liver was uni-

4. Mukherji, S. K.: Far East, Ann. Trop. Med. **4**:54, 1928.
5. Iyer, A. S. V.: Indian M. Gaz. **61**:594, 1926.

formly and smoothly enlarged and there was no wasting or emaciation of the patient after a year's duration of the condition; chronic passive congestion (nutmeg liver), ruled out clinically by the absence of any pathologic cardiac condition or other evidence of cardiac decompensation; tuberculosis of the liver, ruled out by the negative tuberculin skin tests and the absence of any history or signs of tuberculosis in other portions of the body; cystic disease of the liver, ruled out by the absence of any marked irregularity of the enlargement of the liver and the absence of parasites or ova in the stools; amyloid disease of the liver, ruled out by the absence of a focus of chronic suppuration, involvement of the kidneys or edema, and leukemic infiltration of the liver, which was eliminated clinically by the negative results of serologic examinations.

Primary diseases of the spleen were considered in the differential diagnosis, especially Banti's disease. Clinically, the latter was ruled out by the relatively small spleen in proportion to the enormous liver, the absence of signs of portal obstruction and the moderate leukocytosis. Weber [6] emphasized the intimate clinical connection between so-called Banti's disease and "idiopathic nonalcoholic progressive hepatic cirrhosis." In Banti's disease, the morbid process is located mainly in the spleen, and it is always a problem to determine how far the changes in the liver have advanced when splenectomy is advised. Other diseases involving the spleen, such as Gaucher's disease, were eliminated by the negative observations on splenic puncture performed at the time of operation.

ETIOLOGY OF INFECTIOUS CIRRHOSIS

MacMahon [7] recently reviewed the meager literature on infectious cirrhosis. He stated that infectious cirrhosis is one of the less common diseases of the liver, and that it is rarely found in a pure, uncomplicated form, as it occurs more often in combination with the obstructive type. However, he stated that these are not two names for the same entity, and that prolonged biliary obstruction produces fairly constant histologic changes and is not necessarily complicated with infection within the bile ducts.

Mallory stated that of a total of 5,400 postmortem examinations, 1,000 of which were made on children, 45 per cent of the cirrhosis were alcoholic and only 5 per cent infectious.

Mallory and MacMahon both believe that the infection within the terminal bile ducts and the adjacent tissues probably results from an ascending bacterial infection. They have demonstrated organisms in

6. Weber, F. P.: Brit. J. Child. Dis. **20**:78, 1923.
7. MacMahon, H. E.: Infectious Cirrhosis, Am. J. Path. **7**:77, 1931.

the infected portal areas by bacterial stains. In our case, no bacterial stains were made, but cultures of the bile taken at operation were sterile on many mediums. However, the history of an attack of catarrhal jaundice with fever, icterus and gastro-intestinal upset, three years previously, might have been associated with an original duodenitis and cholangeitis, which might have initiated the infectious cirrhotic processes. MacMahon cited five cases in which a history of transient jaundice at an earlier period was obtained. Moon [8] recently reviewed the literature on infection as a cause of juvenile cirrhosis. No definite conclusions were drawn.

Sutton [1] recently reported a case of so-called "primary atrophic cirrhosis" of the liver in a child. He stated:

> It seems likely in the present case that cirrhosis was a sequence of the earlier hepatic infection (so-called infectious jaundice). While such an outcome of what is commonly regarded in children as a comparatively mild disease without serious sequelae is exceptional, it is well to remember that it can occur. Possibly lesser degrees of permanent damage to the liver from catarrhal jaundice are by no means uncommon.

There are several criticisms of his report: He uses the term "atrophic," although, according to the observations at the physical examination, the liver may have been enlarged. The spleen was enlarged and jaundice was present, which is not common in Laennec's cirrhosis. The pathologic report was not detailed enough to rule out infectious cirrhosis. The term "primary" cannot be used when infection is suggested as the etiologic factor. Sutton may have been reporting another case of infectious cirrhosis following after an interval an attack of catarrhal jaundice, as in our case.

THERAPY

When a case of cirrhosis of the large liver type is encountered in a child, such as is described in the case reported, the type of therapy to be instituted depends on the exact diagnosis. As this cannot usually be made clinically, antisyphilitic treatment with mercury and iodides can be tried for a month. If there is no response to this therapy, as indicated by the diminishing size of the liver and lessening of the jaundice, then, in the absence of any marked tendency toward hemorrhage, an exploratory operation may be justifiable, as in our case. If an obstruction of the larger bile ducts (common or cystic duct) is found, it should be properly dealt with. If no obstruction is found, surgical drainage of the gallbladder may be instituted to facilitate drainage of the liver and consequent clearing up of the infection in the terminal bile ducts, on the assumption that the case may be one of infectious

8. Moon, V. H.: Am. J. M. Sc. **177**:68, 1927.

cirrhosis. Histologic examination of a small section of liver removed at the operation will definitely determine the diagnosis. Hanot's and Laennec's types of cirrhosis may run a chronic course, but they are fatal after a number of years.

Apparently in infectious cirrhosis recovery may occur, even after a year's duration, if drainage is facilitated.

Moncrief and Steen[9] also treated a patient with "hypertrophic" cirrhosis (the clinical and pathologic observations practically duplicating those in our case) by surgical drainage of the liver through the gallbladder, with a successful result.

SUMMARY AND COMMENT

1. A rare case of uncomplicated infectious cirrhosis of the liver in a boy 11 years old is reported. There was no familial history of cirrhosis or alcoholism.

2. The etiology of a possible ascending infection is strengthened by the history of an attack of acute catarrhal jaundice several years before the patient was seen by us.

3. The literature on so-called "hypertrophic" and large liver cirrhosis is reviewed and the cases reported in the American literature summarized.

4. The classification of so-called "hypertrophic" cirrhosis is discussed.

5. The clinical and pathologic differential diagnosis is discussed.

6. The advisability of performing an exploratory laparotomy and of taking a section of liver tissue for biopsy is suggested. The favorable response of the patient in our case to surgical drainage of the liver through the gallbladder is reported.

7. It is hoped that attempts will be made in future reports of cirrhosis of the liver in children to classify the condition more accurately as to etiology and pathology and to use the terms "hypertrophic" and "atrophic" merely as descriptive of the stage of cirrhosis rather than of the type.

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9. Moncrief, A., and Steen, R. E.: A Case of Early Cirrhosis of the Liver, Brit. J. Child. Dis. **26**:30, 1929.

EXSTROPHY OF THE BLADDER

COMPLICATED BY OTHER CONGENITAL ANOMALIES *

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An unusual combination of congenital anomalies was found in a baby born at the Mountainside Hospital, Montclair, N. J. The parents were Chinese; the father was 32 years old, the mother 26, and both were apparently in good health. There was one other child, a healthy girl of 5 years. The mother had had no miscarriages, and no history of abnormality on either side of the family was elicited. The mother's pregnancy had been normal, and the baby was born at term. After a labor of thirty hours, the baby was born spontaneously and breathed as soon as delivered. The birth weight was 6 pounds and 10 ounces (3,011 Gm.). One point is worth mentioning: When the mother first came for examination during the third month of gestation, two hairpin pessaries were removed from the cervical canal. They had been inserted over a year before as a means of contraception by a former physician in a distant part of the country. The question arises as to their possible influence on the malformations.

The baby's head, neck, thorax and extremities were entirely normal. A combination of unusual abnormalities was observed on the abdominal wall from the umbilicus to the symphysis pubis. At the point of insertion of the cord on the abdomen, there was a soft tumor-like mass about 3 inches (7.6 cm.) in diameter, covered with cord tissue. Caudad to this tumor was another larger mass, roughly trilobed, covered with raw and bleeding mucous membrane. From the caudad surface of this tumor, slightly to the left of the midline, emerged a flexible tubelike appendage, 3 inches long, also covered with raw and bleeding mucous membrane. Caudad to this tube and connected with it was another smaller trilobed mass, covered with the same bleeding mucous membrane. The two lateral lobes of this mass appeared as two firm spherical masses, about the size of small marbles. The central portion was connected cephalad with the tubelike appendage. No anus was found, but at its usual site in the gluteal furrow there was a small depression. Both urine and meconium dripped constantly from the tubelike appendage. A small catheter was introduced into the orifice of the tube and was felt to pass cephalad up the left side of the larger trilobed ectopic mass. At one time an accidental puncture was made in the right lateral portion of this mass, and urine came from the opening. A small section of the tubelike appendage was cut off and examined histologically and was found to consist of rectal tissue.

The baby appeared vigorous and took the bottle well for the first three days. A Wassermann reaction of the blood was reported negative. As the parents were anxious for the child to live, an operative attempt was made to draw the skin of the lateral portions of the abdominal wall over the ectopic masses. The attempt was unsuccessful as the skin sutures failed to hold. The baby became gradually weaker and died on the twenty-second day after birth. Unfortunately, autopsy was refused.

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* Submitted for publication, March 3, 1931.

This case represents an unusual combination of congenital anomalies. There was an arrest of development of the embryo with a failure to close in the midline from the umbilicus caudad to the spmphysis pubis. Beginning at the cephalad portion of the ectopic mass, there was apparently a large umbilical hernia. Below this hernia, the raw and bleeding trilobed mass represented an exstrophy of the bladder and colon, the former in the right lateral position, the latter in the central and left lateral masses. The tubelike appendage represented a persistent cloaca. The caudad trilobed mass could not be determined definitely, although the central portion probably represented a persistent rectal pouch and the two lateral spherical masses divided portions of the scrotum. In the inguinal regions, on either side of the central masses, the two smooth soft swellings covered with normal skin were probably undescended

Appearance of child.

testes. No x-ray pictures were taken, but by palpation it was felt that the symphysis pubis was open in the midline, as has been found in similar cases. Because of the failure to obtain an autopsy, only the external appearance of these anomalies can be described and their intra-abdominal connections cannot be confirmed. They include an apparent umbilical hernia, exstrophy of the bladder and colon, persistent cloaca, a rectal pouch, undescended testes and divided pubic bones.

REVIEW OF THE LITERATURE

A review of the literature shows that much has been written on this form of congenital malformation, and no attempt will be made to cover the entire field. Von Geldern [1] has written a comprehensive paper on the etiology of exstrophy of the bladder and discussed the various

1. von Geldern, C. E.: The Etiology of Exstrophy of the Bladder, Arch. Surg. **8**:61 (Jan.) 1924.

cases and theories presented by Keith,[2] Wood-Jones,[3] Johnston,[4] Doran [5] and others. Keith and Wood-Jones agreed in believing that the complicated cases of ventral anomalies show a marked similarity and vary only in degree from the simpler cases. Keith gave a classification of the reported cases as follows: (1) ectopia vesicae in the male; (2) ectopia vesicae in the female; (3) ectopia vesicae combined with fistulous condition of the intestines and (4) epispadius.

Keith summarized the conditions found in the complicated cases and stated that the rectum is imperforate, the ileum and cecum enter Meckel's diverticulum or yolk sac, the appendix is bifid, the proctodeum persists, a spina bifida is present, the ureter may enter orifices of the Wolffian duct, and the testes are undescended. All cases have two openings on the central red lobulation; the upper one leads into the small intestine, and the lower one into the large intestine. The large intestine ends blindly in a culdesac in the pelvis. The genital duct and the ureters usually have a common opening on the surface. The pubic bones do not meet in the midline. One kidney is often abnormal.

Wood-Jones expressed the belief that the more complicated cases are manifestations of some process the effects of which are also seen in the uncomplicated cases, and he gave a classification of his own. Johnston reported a case which showed neither spina bifida nor paired diverticula. He did not agree with Keith or Wood-Jones that the complicated cases show a marked similarity. In his case the small intestine opened caudad to the umbilicus; there were also the openings of one blind diverticulum and of the large intestine; there were two separated uteri and vaginae. Doran reported the case of a female fetus in which the anomalies were retroflexion of the spine, spina bifida, exstrophy of the bladder, ectopia viscerum and a short umbilical cord. Von Geldern reported a case of exstrophy of the bladder in which there were three slitlike openings on the central exstrophic mass, the central one leading into a shallow depression, the two lateral ones into longer blind cavities. He expressed the belief that the central depression is a blind bowel, the embryonal postanal intestine, and the two lateral diverticula are buds which are later entirely absorbed by the cloaca and have no fetal homologues. He expressed the belief that these two diverticula and a postanal intestine are present in all cases in varying

2. Keith, A.: Three Demonstrations on Malformations of the Hind End of the Body, Brit. M. J. **3**:1736, 1908.

3. Wood-Jones, Frederick: Extroversion of the Bladder and Some Problems in Connection with It, J. Anat. & Physiol. **46**:193, 1912.

4. Johnston, T. B.: Exstroversion of the Bladder, Complicated by the Presence of Intestinal Openings on the Surface of the Extroverted Area, J. Anat. & Physiol. **48**:89, 1914.

5. Doran, A.: J. Anat. & Physiol. **15**:226, 1881.

forms and are the same structures that Keith called paired appendixes and a blind large intestine. Von Geldern stated that in all cases there is an exstrophy of a retained cloaca as shown by the entire absence of the large intestine and the presence of a common duct for the vas deferens and ureter.

The case under discussion has points of both similarity and difference as compared with the examples already reported. Because of the failure to obtain an autopsy, no complete comparison can be made. It resembled the previous cases in the following details: The umbilical region protuded, was smooth and showed none of the usual puckering, and there was an apparent large umbilical hernia; the exstrophic mass, covered with bleeding mucous membrane, was roughly trilobed and contained bladder and large intestine; the tubelike appendage was retained cloaca; the two lateral spherical masses in the caudad exstrophic tumor were probably divided portions of the scrotum and the central portion a rectal pouch; the testes were undescended, and there was a probable separation of the pubic bones. On the other hand, there was no spina bifida or retroflexion of the spine. Except for the orifice at the end of the tubelike appendage, no other openings were found on the central exstrophic masses, as have always been found in the previous cases reported, representing openings of the small intestine, diverticula and ureters. It is possible that they were overlooked, although a careful examination was made. Nothing can be said about the condition of the intra-abdominal organs.

There is still much disagreement about the etiology of exstrophy of the bladder and its accompanying anomalies. The following causative theories have been presented and discussed by Keith and others and further elaborated by von Geldern: 1. The theory of a rupture: There is a rupture of the anterior wall of the bladder and the adjacent abdominal wall from pressure of retained fluids. However, no obstruction of the genito-urinary tract has been found in these cases. 2. The mechanical theory: Exstrophy is caused by traction of a short umbilical cord. In many of these cases, however, the cord has been found to be of normal length. 3. The transposition of embryonal anlagen: The results are due to a change in position of the vitelline duct. Von Geldern did not see how the vitelline duct can take a position apart from the umbilical cord. 4. The pathologic theory presented by Keith and approved by von Geldern: Toxins from an endometritis or any other form of infection or irritation produce a separation of the lateral walls of the caudal portion of the embryo. Some chemical substance, formed in the uterine mucosa by infection or trauma, is probably the inciting cause. Von Geldern explained this theory as follows: The arrest affects the parts that have not completed their embryonal develop-

ment at the onset of the infection. When the development recommences, certain primitive embryonal structures are maintained and developed as such, and those that should have undergone differentiation, if no arrest had occurred, fail to do so. The spina bifida usually found in these cases results from an arrest in the development of the medullary plate, which leaves the neural tube open. This theory would also explain the retroflexion of the spine as that is the position the embryo normally assumes. The caudal part of the embryo acquires its tubal form later than the cephalic part, showing that the arrest occurs before this tubal form has been completed. Von Geldern expressed the belief that the arrests all occur at approximately the same period of the embryonal development, and the degree of the arrested development depends on the concentration of the chemical substance to which the embryo is subjected. In support of this theory he quoted experiments by Morgan and Hertwig, who produced spina bifida by subjecting frogs' eggs to the action of 0.6 and 0.7 per cent solutions of sodium chloride.

If the chemical theory of arrested development of the embryo by the action of toxins of an endometritis is correct, it is well to consider in the present case what causative action the hairpin pessaries in the cervical canal may have had on the resulting anomalies. They had been introduced into the cervix more than a year before the beginning of this pregnancy and remained there until the end of the third month. It is possible or even probable, in the light of the pathologic theory, that the pessaries caused an endometritis which resulted in the early arrest of development of the fetus. This action cannot be proved, but it is worth careful consideration.

PRECOCIOUS MENSTRUATION *

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DURHAM, N. C.

History.—A 5 year old white girl, who presented many interesting sociological as well as diagnostic problems, was admitted to the Duke Hospital on Dec. 4, 1930, with the complaint of menstruation since the age of 3 months and overdevelopment.

The mother, 27 years of age, was living and well; menstruation had begun at the age of 14 years. The father, aged 27, was also living and well. Both parents were average in size. There was one other child in the family, a boy 4 years old, normal in size and development, and weighing 34 pounds (15.4 Kg.). There was no family history of any condition similar to the patient's.

The patient was born on July 28, 1925. Delivery was spontaneous at full term. The birth weight was 6¾ pounds (3.1 Kg.). The infant had a small amount of vaginal bleeding every two or three days from birth to the age of 1 month. Feeding was uneventful. She sat alone, walked and talked at a normal age; there was enuresis up to 4 years of age. There had been no illness, except mumps and otitis media. Except for the vaginal bleeding, the baby grew and developed normally until the age of 3 months, when she had a period of vaginal bleeding that lasted for three days. These periods recurred every thirty days until the age of 1 year. The amount of blood lost was equivalent to that of the normal menstrual flow of a 15 year old girl. Between the ages of 1 and 4 years the intervals were longer, from one to two months, and the duration of the individual periods was longer, from four to five days. During 1930 (fifth year of age), the child menstruated only three times, in March, June and on October 25. During the first two days of the periods, she had cramps in the lower part of the abdomen.

At the age of 14 months her breasts were noticeably large, and they had grown abnormally since. There was no abnormal growth or distribution of hair. She had always had a tremendous appetite and had grown rapidly since the age of 8 months. Her mother stated that she gained 4 pounds (1.8 Kg.) between the ages of 13 and 14 months. She had always had large hips, the general contour of an adult woman, rather than that of a child, and a very deep voice. She had always been bright, sensitive, restlessly active, wilful and difficult to discipline.

Examination.—The temperature was 37.2 C. (98.6 F.); the pulse rate, 88; the respiratory rate, 20, and the blood pressure, 100 systolic and 75 diastolic. The patient had the height of a 10 year old child but the general contour of a diminutive adult (fig. 1). Her arms and legs were slightly short in relation to her body. She had normal intelligence for a child of 5 years and was alert and active. She was affectionate to the point of being highly sexual. Her skin was smooth and moist. There was no increase in the growth of hair nor any axillary or pubic hair. The breasts were as large as those of a girl of 15 years. The areolae were pinkish brown and the nipples protruding.

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* From the Department of Pediatrics, Duke University School of Medicine.

Pelvic examination was conducted under gas anesthesia. The clitoris was not enlarged; the labia were large and well developed. The vaginal orifice admitted one finger with ease, and two could be inserted. The cervix was very large and firm and pointed posteriorly. The uterus was in good position, freely movable, of adult size, and uniformly enlarged. Both ovaries could be felt; the left was larger than the right.

Fig. 1 shows the patient in the center with a normal 5 year old girl on the right and a normal 7 year old girl on the left. A comparison of measurements of the 5 year old child with those of the patient is given in table 1.

The results of the remainder of the physical examination were negative.

Laboratory Examinations.—The red blood cells numbered 6,460,000, and the white blood cells, 15,900; the differential count was normal; the hemoglobin content

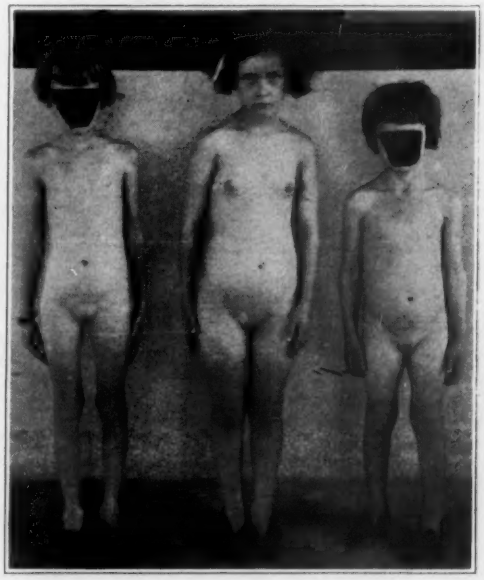

Fig. 1.—The patient is seen in the middle with a normal 5 year old girl on her left and a normal 7 year old girl on her right.

was 95 per cent. Examination of the urine and stools gave negative results. The Wassermann reaction of the blood was negative. Chemical analysis of the blood showed: calcium, 9.5; phosphorus, 4.6; nonprotein nitrogen, 31 mg. per hundred cubic centimeters. Dextrose tolerance tests gave the following results: (1) fasting, 105 mg.; (2) 154 mg.; (3) 125 mg., and (4) 118 mg. per hundred cubic centimeters. The basal metabolic rate could not be satisfactorily determined because of a lack of cooperation. A roentgenogram of the skull showed nothing abnormal. The sella turcica appeared normal in size and shape; the chest was clear; the long bones were large for the patient's age, and the epiphyses were more nearly closed than is normal at this age. Ascheim-Zondek tests were done on the patient's urine; the results were inconclusive.

On December 20, an exploratory laparotomy was performed. Normal suprarenal glands, an adult-sized uterus and two adult-sized ovaries were found. One

half of the left ovary and a small piece of the right ovary were removed for study. The fimbriated ends of the tubes were buried. A normal appendix was removed. (Sterilization was done at the request of the parents.)

Pathologic Report.—A single entire ovary would have measured 3 by 2 by 1.5 cm. The ovaries on gross examination presented a smooth white surface, with several small projecting bluish cysts. Microscopically, the small bluish areas were follicular cysts. They were lined by cuboidal epithelium. Numerous growing follicles were seen with ova surrounded by several layers of granulosa cells. In some of these the theca interna was several cell layers thick. The right ovary

TABLE 1.—*Comparison of Measurements of a Normal 5 Year Old Child with Those of the Patient*

	Patient	Normal
Weight	30 Kg.	19.3 Kg.
Height	130 cm.	112 cm.
Head, circumference	52 cm.	49 cm.
Arm span	125 cm.	112 cm.
Chest, circumference	63.5 cm.	59.5 cm.
Bust	63 cm.	58.5 cm.
Waist	60 cm.	56 cm.
Hips	71 cm.	57.5 cm.
Shoulder, circumference	75 cm.	70 cm.
Upper arm, circumference	19.5–19.5 cm.	16 –16 cm.
Lower arm, circumference	18 –18.5 cm.	16 –16.5 cm.
Mid thigh, circumference	39.5–40.5 cm.	30.5–30.5 cm.
Lower leg, circumference	26.5–26.5 cm.	20.5–20.5 cm.
Pelvic measurements		
Spines	22 cm.	17 cm.
Crests	22.5 cm.	17.5 cm.
Trochanters	24 cm.	19 cm.
Anteroposterior	14.5 cm.	11.5 cm.

TABLE 2.—*Precocious Menstruation in Gautier's Series*

Age at Onset of Menses	Cases	Duration of Regular Menses	Cases
First year	5	3 months	3
Second year	4	5 months	3
Third year	5	6 months	2
Fourth year	4	1 year	2
Fifth year	4	2 years	1
Sixth year	4	4 years	1
Seventh year	4	5½ years	1
Under 1 year	5		

contained a typical corpus albicans (fig. 2). The hyaline-festooned appearance was characteristic.

The patient had an uneventful recovery from her operation, and was discharged from the hospital on Jan. 6, 1931.

Since discharge she has menstruated three times. At the time this paper was written she was being given deep roentgen treatments to produce a temporary amenorrhea.

COMMENT

A number of quite similar cases have been reported in the literature. Morse,[1] in 1897, described a 14 months' old child in whom menstruation began at the age of 9 months. Gautier, cited by Morse,

1. Morse, J. L.: Precocious Maturity, Arch. Pediat. **14**:241, 1897.

reported twenty-four cases in 1884. A summary of his findings is given in table 2.

Each of Wolff's [2] and Haller's [2] patients menstruated at the age of 2 years, while Haller's patient became pregnant at the age of 8 years. Prochownick,[3] Nacke.[4] Stoeltzner [5] and Munzer [6] also reported cases. None of these discussed the cause of the condition. Riedel [7] reported a case that was due to an ovarian sarcoma.

Some authors have attributed the syndrome of precocious menstruation to pineal disturbances. Bailey and Jelliffe [8] reviewed fifty-

Fig. 2.—Photomicrograph of the right ovary; a corpus albicans can be seen in the middle of the field.

2. Quoted by Falta, W.: Endocrine Diseases, London, J. & A. Churchill, 1923, pp. 434-435.

3. Prochownick: Fall von Menstruatio praecox, Arch. f. Gynäk. **17**:330, 1881.

4. Nacke: Menstruatio praecox, Zentralbl. f. Gynäk. **32**:1116, 1908.

5. Stoeltzner: Menstruatio praecox, Med. Klin. **4**:5, 1908.

6. Munzer, A.: Pubertas praecox und psychische Entwicklung, Berl. klin. Wchnschr. **51**:448, 1914.

7. Riedel, H.: Menstruatic Praecox und Ovarialsarkom, Wien. klin. Wchnschr. **9**:942, 1904.

8. Bailey, P., and Jelliffe, S. E.: Tumors of the Pineal Body, Arch. Int.Med. **8**:851 (Dec.) 1911.

nine cases of pineal tumors. Of the patients showing sexual precocity, or "pubertas praecox," none were girls. Horrax and Bailey [9] collected from the literature between 1892 and 1924 fourteen cases of premature sexual development due to pineal disturbances. All of the patients were males. Cushing [10] expressed the belief that the pineal syndrome as such is secondary to hypophyseal disturbance. "Pineal syndrome has occurred only in such cases of pineal tumors as have led to an obstructive hydrocephalus and thus of necessity to secondary hypophyseal disturbances."

Cushing [11] and Goetsch,[12] in 1913, fed anterior lobe of the pituitary to young rats, and found that it had a stimulating effect on the growth and development of the reproductive glands, causing early and frequent breeding. Control experiments in which posterior lobe of the pituitary and ovarian extract were fed to young rats gave negative results.

The more recent work on the anterior lobe of the pituitary has shown that there are two hormones produced by this gland. One is growth-promoting, and the other is gonad-stimulating. These two hormones are antagonistic, and in the normal person there is maintained a perfect balance between them. In the case here reported, there was obviously a great excess of gonad-stimulating substance and also an increased amount of a growth-promoting hormone, though to a lesser degree.

The patient differs from those whose abnormalities are due to disturbances of the suprarenals, because of the absence of an excessive growth of hair. This child had no pubic or axillary hair and no increase of hair over the body and arms. Also, at operation the suprarenals were found to be normal. It is hard to believe that this disturbance is primary in the ovary. The pathologic sections showed nothing to account for the picture, except indirectly. The ovaries were normal in every way, except that they were mature. It is also difficult to correlate the excessive bodily growth with ovarian disturbance.

The possibility of a pineal origin of the trouble is doubtful; all of the pineal cases so far reported have been in boys. Further evidence against this supposition is that there were no signs of an intracranial tumor, which is the usual way in which the pineal gland is affected.

It is likely that hyperfunction of the anterior lobe of the pituitary, with a greater production of the gonad-stimulating hormone than

9. Horrax, G., and Bailey, P.: Tumors of the Pineal Body, Arch. Neurol. & Psychiat. **13**:423 (April) 1924.

10. Cushing, quoted by McCord, C. P.: Pineal Gland and Sex, J. A. M. A. **65**:517 (Aug. 7) 1915.

11. Cushing, H.: Pars Anterior and Its Relation to Reproductive Glands, Proc. Soc. Exper. Biol. & Med. **11**:26, 1913.

12. Goetsch, E.: Surg., Gynec. & Obst. **25**:229, 1917.

of the growth-promoting one, will account for all of the factors in this case. The precocious maturity of the ovaries, with consequent ovulation and menstruation, is secondary to the disturbance of the anterior lobe of the pituitary.

SUMMARY

1. A case of precocious menstruation is reported, with results of an exploratory abdominal operation and pathologic studies of both ovaries.

2. Evidence found in experimental work in cases previously reported and the findings in this case point to a diagnosis of hyperpituitarism, confined to the anterior lobe, with an imbalance of the two hormones produced by it.

PREMATURE SEXUAL DEVELOPMENT IN CHILDREN DUE TO MALIGNANT OVARIAN TUMORS

WITH SPECIAL REFERENCE TO HORMONAL STUDIES AND AFTER-TREATMENT *

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A considerable number of malignant tumors of the ovary in young children have been described. A small number are accompanied by premature sexual development, which, due to the fact that recession of prematurity takes place after the removal of the tumor, must be ascribed to the influence of the ovarian growth. Not every tumor of the ovary in children, however, irrespective of whether it is malignant or benign, produces pubertas praecox. On the other hand, activation has been noted with various histologic types of malignancy. In my own experience both a carcinoma and a teratoma of the ovary proved to be the underlying cause of prematurity. In one other case in which a carcinoma of the ovary was present without premature sex development, considerable female sex hormone was noted in the urine, a finding that I have never observed in normal children. An excess of female sex hormone in the urine and blood has been reported in women and men afflicted with cancer,[1] although my own investigations have not confirmed these findings.

Reviews of the literature were published by: Wiel [2] in 1905, reporting twenty-two cases of malignant tumor; Harris [3] in 1925, reporting twenty-one cases of teratoma; Downes [4] in 1921, reporting sixteen cases of malignant tumor, and Reuben and Manning [5] in 1922, reporting cases of growth producing pubertas praecox.

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* Submitted for publication, June 27, 1931.

* From the Gynecological Service and the Division of Laboratories, Mount Sinai Hospital.

1. Dingemanse, E.; Freud, J.; de Jongh, S. E., and Laquer, E.: Ueber das Vorkommen von hohen Mengen weiblichen (Sexual-) Hormons Menformon im Blut von Krebskranken (Männern), Arch. f. Gynäk. **141**:225, 1930.

2. Wiel, H. I.: A Survey of Ovariotomy at Extremes of Life, Bull. Johns Hopkins Hosp. **16**:102, 1905.

3. Harris, R. H.: Carcinomatous Teratoma with Premature Puberty and Precocious Somatic Development, Surg., Gynec. & Obst. **4**:191, 1925.

4. Downes, W. A.: Tumors of the Ovary in Children, J. A. M. A. **76**:443 (Feb. 12) 1921.

5. Reuben, M. S., and Manning, G. R.: Precocious Puberty, Arch. Pediat. **39**:769, 1922.

Based upon such statistics [6] as give a pathologic diagnosis, the various histologic types are represented by eighteen sarcomas; six carcinomas; three teratomas and two chorionic epitheliomas. A report of my own cases follows.

REPORT OF CASES

CASE 1.—The first patient, M. B., admitted in March, 1930, was an exceptionally well developed girl, 9½ years old, in perfect health until three days before admission. The breasts were those of a girl of 14 to 15 years and the general appearance that of a child at least two or three years older than the actual age of the patient. The pubic and the axillary hair were well marked. Three days before admission, the child was seized with severe cramplike pain in the lower part of the abdomen, which continued intermittently. There was bleeding from the vagina. On admission, the temperature was found to be 102 F. The other findings were vomiting and a tender abdomen with shifting dulness in the flanks. On the seventh day the temperature had dropped to below 100 F., and operation was performed. An ovarian tumor was found on the right side, with a twist of its pedicle. The tumor was hemorrhagic, owing to infarction. It was about the size of a grapefruit and reached half way to the umbilicus. Convalescence was uneventful. At the time of this report, more than a year after operation, the child is in perfect health.

The tumor had a hard, smooth surface, with sharp edges. Examination revealed it to be a malignant teratoma. The mesoderm was represented by sarcoma-like tissue, cartilage and bone, and the entoderm by small cystic cavities lined with ciliated epithelium. The ectoderm appeared in the form of carcinoma-like areas.

The after-treatment will be discussed later.

CASE 2.—The second patient, S. M., was a diminutive colored girl, aged 8 years. She showed no signs of premature sexual development. She had been well until three days before admission, at which time she complained of pain in the lower part of the abdomen.

Examination in March, 1930, revealed a mass in the midline of the abdomen, reaching to the umbilicus, and extending down into the pelvis, situated somewhat more to the right than to the left side. The mass bulged into the cul-de-sac, where a diminutive uterus was felt behind it. The mass itself was hard and not movable. Operation, performed the day after examination, revealed a nonadherent tumor the size of a large grapefruit, arising from the right ovary. A right salpingo-oophorectomy with partial amputation of the cornual portion of the uterus was performed. Convalescence was uneventful.

The pathologic report of the tumor showed it to be a medullary carcinoma. At the time of this report, one year after operation, the patient is well.

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6. Freund, E.: Case of Teratogenous Chorionepithelioma of Ovary in Child, Frankfurt Ztschr. f. Path. **38**:313, 1929. Harvey, W. G.: A Case of Precocious Sexual Development, Irish J. M. Sc., Feb., 1923, p. 550. Hunt and Simon: Ovarian Cancer in Infancy, Ann. Surg. **87**:84, 1928. Jaisohn, P.: Sarcoma of Ovary in Child Eight Years Old, J. A. M. A. **95**:1097 (Oct. 11) 1930. Lanman, T. H.: Tumors of Ovary in Childhood with Report of five Cases, New England J. Med. **201**:555, 1929. Read, C. D.: Specimen: Chorion-Carcinoma of Ovary with Torsion of Pedicle in Child Aged eleven, Proc. Roy. Soc. Med. (Sect. Obst. & Gynec.) **21**:67, 1928. Southam, A. H.: Ovarian Sarcoma in Child Associated with Sexual Precocity, Brit. M. J. **1**:661, 1928.

CASE 3.—Permission to cite the aspects of the third case was granted by Dr. Clarence B. Ingraham and Dr. A. C. Eastlake of Denver, in whose practice this patient was observed. Premature puberty with menstruation was noted in a child 3 years old. At operation a large ovarian tumor was successfully removed. Convalescence was uneventful, except for a streptococcus infection of the abdominal wall.

A portion of this tumor was given to my collaborator, Dr. R. G. Gustavson, who performed a lipoid extraction of the tumor tissue and sent it to me for assay. The sections of the tumor, which I had the opportunity of studying, proved to be those of an embryonal alveolar carcinoma. The biologic significance of this growth will be discussed in a later paragraph.

THE USE OF ROENTGENOTHERAPY IN CHILDREN

From a study of the literature, it is apparent that carcinomas and teratomas in children are extremely malignant and, except in a few instances, recur within a comparatively short time (Harris [3]). Under these circumstances, although I was fully aware of the drawbacks of giving postoperative roentgen therapy, this was done in the case of the two patients under my care, who, although the tumors by all histologic criteria were extremely malignant, have remained well for at least a year. The two children, M. B. and S. M. (cases 1 and 2), each received the full dosage necessary for carcinoma.

It was well understood that the danger of producing eunuchoidism in the children had to be weighed and balanced against the danger of recurrence. Dr. S. G. Berkow compared the measurements and proportions of these children one year after operation with those obtained immediately postoperatively. He noted an increase in the length and proportions of the upper extremities, but considered these changes by no means indicative of abnormality. Further observation during the course of the next few years will be necessary to settle this point definitely.

In sharp contrast with the course in these two children is a case that I am able to mention through the kindness of Dr. A. V. Moschcowitz, who operated two years ago on a girl of 13 years, removing a malignant teratoma of the ovary. No metastases were found at operation. I strongly advised roentgen therapy, with which opinion Dr. Moschcowitz concurred. Another opinion, however, was sought, and the parents were terrified by the fear of eunuchoidism following the roentgen treatment, as pictured to them by a prominent consultant. This girl died eight months after operation with multiple metastases throughout the abdomen and chest.

In order to emphasize further the advisability of postoperative roentgenotherapy, I may mention another instance of a tumor occurring in a child of 8 years, although this tumor did not arise from the ovary.

REPORT OF CASE

There was a history of swelling of the abdomen for the last four weeks, with the loss of weight and severe cramplike pains for two weeks. This child was in a desolate condition, with shrunken limbs, wrinkled skin and a tremendously distended abdomen due to a large tumor mass reaching almost to the xyphoid. The sole area of tympany was limited to the extreme upper part of the abdomen. An exploratory laparotomy was performed by me in November, 1929. This revealed a large friable myxomatous growth, extremely vascular, developed mainly retroperitoneally and occupying the mesentery of the sigmoid, extending behind the descending colon, and also into the mesentery of the small intestine to within 1 inch (2.5 cm.) of the intestinal margin. The growth ruptured during operation, and, to prevent death on the table, a gauze pack was introduced into the bleeding area and led out through the lower portion of the abdominal incision. An absolutely hopeless prognosis was given. When the drain was removed, some of the tumor material pouted out of the abdominal wall. Examination of material removed at operation showed a mesenchymal myxomatous growth classified as a myxosarcoma. In order to leave no therapeutic measure untried, roentgenotherapy was applied to the abdomen. The growth rapidly regressed, and at the time of this report, one and one-half years after operation, the child is in blooming health with not the slightest evidence of recurrence. This child too, as yet shows no sign of eunuchoidism.

Under the circumstances, I feel, even more strongly than before, that roentgenotherapy is indicated postoperatively in malignant tumors of the ovary in children, irrespective of whether the future follow-up may show that eunuchoidism develops. It is too early to form any definite opinion as to whether any ovarian reformation may take place.

THE BIOLOGIC SIGNIFICANCE OF OVARIAN GROWTHS IN CHILDREN

From a study of the three cases available, the following has been learned: Although concentrated extracts of the ovary of fetuses and children do not show the presence of female sex hormone in demonstrable quantity, female sex hormone was recovered from the ovary in a case of embryonal carcinoma in a child of 3 years (case 3).

A study of the urine of the patients in cases 1 and 2 showed the presence of female sex hormone in the urinary excretion for one week postoperatively. All of our studies with improved methods on a limited number of children before the age of puberty have given negative results. From these investigations it follows that ovarian growths may activate the hormone production of the ovaries in children long before puberty. This activation disappears within two weeks following the removal of the tumor. That such activation may occur from unknown causes without the presence of tumor has long been known. Examination of an unpublished case of pubertas praecox in a girl aged 3 years was made possible through the cooperation of Dr. B. Schick and Dr. H. Schwartz. In this child cyclic excretion of female sex hormone through the urine has been observed during two of her somewhat irregular menstrual cycles.

SUMMARY AND CONCLUSIONS

1. The solid ovarian tumors occurring in childhood are extremely malignant. Their removal should be attempted as soon as the diagnosis can be made.

2. Postoperatively, intensive roentgenotherapy is recommended in order to avoid recurrence. Roentgenotherapy is also indicated if only partial removal of the growth is feasible or if operation is found to be impossible.

3. Ovarian tumors may activate the prepuberal ovary to such a degree as to produce premature sexual maturity, or to a less degree, which is recognizable only by biologic tests performed on the urine. It appears unwarranted to attempt to perform a blood test, as 40 cc. of blood is too large a quantity to remove from these debilitated children.

4. In cases of abdominal tumor in children, the female sex hormone test performed on the urine may help in localizing the origin of the growth in the ovaries unless further studies, for which no opportunity has presented itself as yet, show that malignant tumors elsewhere also cause the appearance of female sex hormone in children.

Progress in Pediatrics

AGRANULOCYTOSIS

REPORT OF A CASE, WITH AUTOPSY OBSERVATIONS *

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Recently Bigler and Brennemann [1] have reported ten cases of "sepsis with leukopenia" in children. They believe that this disease is a clinical entity characterized as follows: gradual onset, fairly short course with fatal termination, fever, severe anemia, petechial hemorrhages with a low platelet count and leukopenia with a decrease in granulocytic cells. An excellent discussion of the differential diagnosis of aleukemia, leukemia and other blood diseases showing a somewhat similar picture is given in this paper. The present case is being reported not only because of the rarity of the condition, but because our patient has been under careful observation in an earlier stage of the disease than in the cases previously reported. Roberts and Krache [2] have recently reported a carefully observed case of agranulocytosis in an adult, in which daily blood counts were made through two successive attacks of the disease. They have presented evidence from other reports and from their own study to show that the attacks have three onsets: a marrow onset, a blood stream onset and a clinical onset. The blood stream onset apparently follows the marrow onset by three or four days, and the clinical onset came four days after the blood stream onset in their case. Our case seems to illustrate the same sequence of events, but we believe that we have also been able to show a similar sequence in remissions induced by blood transfusions (fig. 1). Roberts and Krache were inclined to attribute the remission in their case to the leukotactic effect of a septicemia that developed when the polymorphonuclear count became very low. However, it may be significant that a blood trans-

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1. Bigler, J. A., and Brennemann, J.: Sepsis with Leukopenia in Children, Am. J. Dis. Child. **40**:515 (Sept.) 1930.

2. Roberts, S. R., and Krache, R. R.: Agranulocytosis, J. A. M. A **95**:780 (Sept. 13) 1930.

fusion was given the day before the first significant rise appeared in the neutrophil count.

REPORT OF CASE

History.—The patient was born at term and had made an uneventful progress in development throughout the first year of his life. He was the only son of healthy, intelligent, cooperative parents who had placed him under the care of a pediatrician throughout infancy. He was breast-fed for nine months, then received certified raw cow's milk for two months and had been taking raw milk, which was not certified, ever since. At the age of 18 months he had a fever lasting two weeks and reaching a peak of 103 F. The fever was attributed to teething by the attending physician. During the winter of 1929, at the age of 2½ years, he was exposed to the fumes given off by a burning gas furnace for about three weeks. The fumes escaped into the house through a defective flue located in the basement, and the patient was exposed more than any other member of the household as he was home all day and was kept in the house during the cold weather. The mother, who was home only on Saturdays, noticed that she developed a headache while working in the kitchen on three successive Saturdays, and this eventually led to an investigation of the gas furnace. The patient never became unconscious, nor did he show any other symptoms except alternating periods of drowsiness and irritability during this period.

Examination.—Our observation of the boy dates from April 11, 1930, at the age of 3½ years, when one of us was called to see him because he had been limping for one day. At that time he was afebrile, but showed tenderness to extreme flexion, extension and abduction of the right hip.[3] A temperature record was kept (at least two readings daily) from this time on. The tenderness in the hip joint apparently disappeared in a few days as the patient was then up, walking and running around without a limp. From April 21 until April 30, he ran a low grade fever, the highest reading being 103.4 F. per rectum. During this time there were no symptoms, and it was difficult to keep the patient in bed. On April 23, there was a small pinhead-sized ulcer of the gum in the labial fornix near the base of a lateral incisor tooth, and the lymph glands in the anterior cervical triangle were slightly larger than at the previous examination. The ulcer healed in a few days, but the fever continued, and a careful examination, including a urinalysis, gave no explanation for the fever. The patient was apparently feeling fine. A blood count was made on April 28, with the following results: red cells, 3,910,000; white cells, 5,600. A differential count showed: neutrophils: stab forms, 2 per cent; segmented forms, 4 per cent; total, 6 per cent; lymphocytes: large, 14 per cent; small, 76.5 per cent; monocytes, 2.5 per cent; lymphoblasts or myeloblasts, 1 per cent.

Course.—After April 30, the patient seemed well in every way and was allowed to be up. Although his parents observed him carefully and were repeatedly questioned, they were unable to detect anything abnormal in his behavior during this afebrile period, which lasted until July 26, when his temperature again rose to 101 F., and the mother noticed that one of the lymph glands in the neck was slightly swollen. He was again seen by one of us on August 1, but there was no enlargement of the lymph glands. Another blood count on this date gave the following results: hemoglobin, 70 per cent (Tallqvist); white cells, 2,700. A differential count showed: neutrophils, 2 per cent; myelocytes, 1 per cent; lymphocytes, 93 per cent; lymphoblasts or myeloblasts, 5 per cent.

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3. Pain in one or more joints, without swelling or redness, was an early symptom in some of the cases reported by Bigler and Brennemann.

A record of the white blood cell counts, body temperature and treatment throughout the remaining course of the illness is shown in figure 1. The patient did not show any subjective symptoms other than the initial transitory limping until August 5, when he began to be listless; a few days later he became irritable, and a slight serous nasal discharge and a small crusted abrasion on the nasal

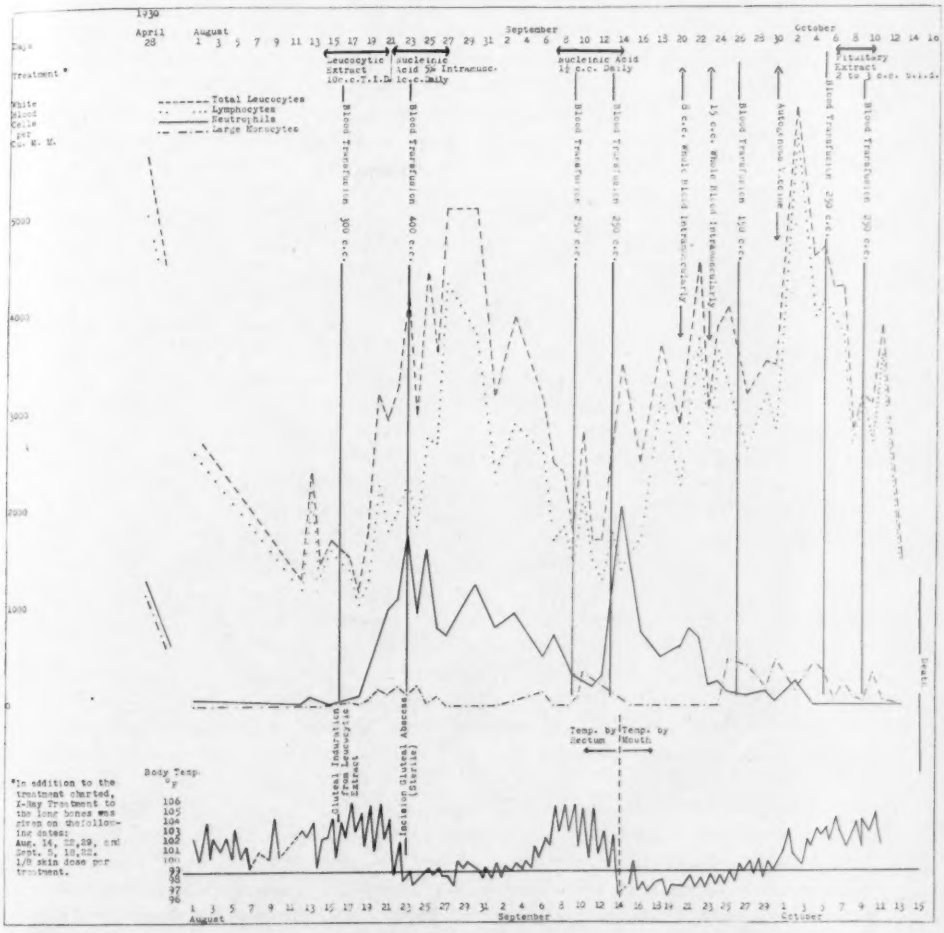
1930
April 28
August
September
October
Total Leucocytes
Lymphocytes
Neutrophils
Large Monocytes
Leucocytic Extract 10c.c. I.V. Daily
Nucleinic Acid 5% Intramusc. 1 c.c. Daily
Nucleinic Acid 12 c.c. Daily
Pituitary Extract 2 to 3 c.c. b.i.d.
Blood Transfusion 300 c.c.
Blood Transfusion 400 c.c.
Blood Transfusion 250 c.c.
8 c.c. Whole Blood Intramuscularly
15 c.c. Whole Blood Intramuscularly
Blood Transfusion 150 c.c.
Autohemotherapy
Blood Transfusion 250 c.c.
Blood Transfusion 300 c.c.
Gluteal Induration from Leucocytic Extract
Incision Gluteal Abscess (Sterile)
Temp. by Rectum
Temp. by Mouth
Body Temp. °F
*In addition to the treatment charted, X-Ray Treatment to the long bones was given on the following dates: Aug. 14, 22, 29, and Sept. 5, 12, 22. 1/8 skin dose per treatment.

Fig. 1.—Record of the white blood cell counts, body temperature and treatment.

septum developed. On August 15, the right tonsil was larger than at previous examinations and slightly injected. It was even larger the next day, but rapidly diminished after the blood transfusion and gargling with sodium perborate. During this febrile period, a sterile abscess was produced by one of the injections of leukocytic extract. It may have had something to do with the remission that soon occurred, but no abscesses were produced in subsequent periods of sepsis, which were also followed by remissions. Just prior to the first blood transfusion, an unusual amount of bruising (purpura) was noted at the site of puncturing the skin

for blood counts. This rapidly disappeared after the transfusion. On September 9, during the height of his third attack, similar (but less severe) purpuric manifestations were present. Then again, a few days before death, a purpuric spot appeared on the upper lip.

A graphic comparison of the neutrophil count with the temperature record shows that during the remission, when the temperature was either normal or subnormal, the total neutrophil count was gradually falling. Toward the end of each remission, as the neutrophils were reaching a level below 600 cells per cubic millimeter, the temperature began to rise. Although a moderate congestion of the turbinates of the nose appeared concomitant with the rise in temperature, it was only after the patient had been running a temperature for several days that a slight nasal discharge was observed and a slight enlargement and hyperemia of the tonsil developed. Perhaps these signs of infection in the nose and throat might have appeared earlier if a gargle of sodium perborate had not been used three times daily. With each attack the red blood cell count and hemoglobin gradually started to fall a few days after the fever began. The repeated transfusions kept the red cells at a fairly satisfactory level, however. The lowest red count was 1,930,000, and the lowest hemoglobin, 35 per cent, both of these determinations having been made just prior to the second blood transfusion. The color index hovered around 1, the lowest reading being 0.7, and the highest, 1.2. Nucleated red cells were very scarce, as were also the myelocytes, which appeared only at the onset of a remission. However, the polymorphonuclear neutrophils in the peripheral blood were all comparatively "young forms," most of them having two lobes. Polymorphonuclears with three lobes were seldom found, and at no stage of the disease were four lobes observed. On the other hand, juvenile and stab nuclei were more common. Further evidence of the profound changes in the granulocytes in this disease was found in the altered cell morphology. In the normal development of the granulocyte, the granules develop during the myelocyte stage, and although the granules stain fainter and fainter as the leukocyte grows older, it is not until the last degenerating stage of its development (the terminal nonmotile phase), that there is no staining reaction at all. In the first blood smear examined in this case on April 28, the granules were found to be either invisible or absent in a few of the granulocytes. On September 1, one week after the onset of the most prolonged remission observed, nearly all the neutrophils had stained granules, but the percentage of cells showing granules decreased rapidly thereafter until September 8, when most of them showed no granules. These blood smears were all stained with Wright's stain, a standard technic being used.

The border of the spleen became palpable at the height of the third febrile period, but it receded during the remission and was never very markedly enlarged. In spite of the periods of severe sepsis, the patient regained his weight between attacks of fever and was well nourished throughout the course of the disease. On September 11, he began to complain of pain on defecation and every time his temperature was taken by rectum. We have no reason to suppose that he had had any rectal trouble previous to this time, as he had been having regular pasty stools daily and had been having his temperature taken rectally at least twice a day since April. Examination of the rectum with a proctoscope on September 14 disclosed the presence of a firm, rounded, slightly hyperemic mass, about the size of a pea, attached to the anterior wall of the rectum just within the sphincter. Although the possibility of this being an abscess was considered, it was thought best to treat it expectantly. The child was taught to have his temperature taken by mouth, and in a few days all symptoms referable to this area had disappeared. A blood culture taken on September 29 showed no growth. The skin had a lemon yellow

tint of varying intensity throughout the course of the disease. During the first febrile attack it was so slight that it could not be called abnormal. He was very blonde and had received considerable heliotherapy. A few days before the end, which occurred during the fourth febrile period, an icteric tint began to develop, and the patient was quite markedly jaundiced on the day of his death, Oct. 15, 1930.

Postmortem Observations.—The body was that of a well developed and well nourished male child and weighed 22 Kg. The integument was a lemon yellow. The conjunctiva, bulbi and sclera were slightly yellow. The mouth and nostrils were covered with a dark brownish-red material. The scrotum was markedly edematous. The subcutaneous fat tissue over the chest and abdomen was about 1.5 cm. thick and of a deep lemon color. The muscle tissue was moist and brownish red. When the abdominal cavity was opened, the small pelvis was found to be

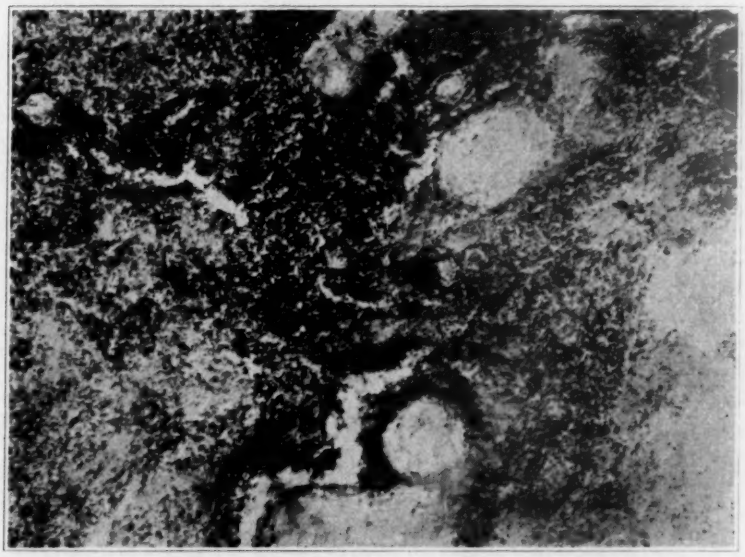

Fig. 2.—Section of the necrotic submucosa of the rectum, showing thrombosed vessels and myriads of micro-organisms. There was no cellular reaction. Giemsa stain.

filled with about 350 cc. of a deeply hemoglobin-stained, thin fluid. The abdominal organs were in normal relation. The visceral and parietal peritoneum were smooth, moist and glistening. The intestines were markedly distended and of a pale yellow color. The liver was about 1½ inches (3.77 cm.) below the costal margin. The omentum contained a moderate amount of yellowish stained fat. The spleen was moderately enlarged and firm. The mesenteric, retroperitoneal, gastric and hepatic lymph nodes were not enlarged; some were pinkish gray and others brownish red. The diaphragm was at the lower border of the fourth rib on both sides. When the thoracic cavities were opened, it was found that the left pleural cavity contained about 50 cc. and the right about 20 cc. of a hemoglobin-stained fluid.

The thymus weighed 5.72 Gm. The parenchyma was a pale grayish red and on section was moist. Macroscopically, it was without change.

The thyroid weighed 3.5 Gm. The parenchyma was brownish red, with a normal amount of colloid.

The right lung weighed 147 Gm., and the left, 149 Gm. The upper lobes were fluffy and a pale grayish red, with a slight yellowish tinge. There were a few groups of dark bluish-violet lobuli here and there. On section, the upper lobes contained air everywhere, and on pressure, a frothy, hemoglobin-stained fluid dripped off. Both lower lobes were of a semisolid consistency and mottled dark bluish violet. On section, the cut surface was smooth and dark brownish red. On pressure, a thick, deeply hemoglobin-stained fluid dripped off. The bronchial lymph nodes were not enlarged. On section, they were moderately anthracotic. The bronchi contained some dark brownish-red mucus. The mucosa was smooth and a pale grayish yellow.

Fig. 3.—Section of the submucosa of the rectum, showing a few histiocytes and numerous micro-organisms.

The heart weighed 104 Gm. The pericardial sac contained about 15 cc. of a light hemoglobin-stained fluid. The visceral and parietal pericardium was smooth, moist and glistening. When the heart was opened, it was found to contain about 50 cc. of almost completely hemolyzed blood and some brownish-red blood clots. The wall of the left ventricle was about 8 mm. thick, and that of the right ventricle, about 3 mm. The myocardium was a dull reddish brown, with a tinge of yellow, and was very flabby. The valves, endocardium of both ventricles, auricles and conus arteriosus were diffusely hemoglobin-stained. The valves were without change.

The spleen measured 13 by 8 by 4 cm. and weighed 162 Gm. The capsule was stretched, smooth, transparent and a dark bluish violet. On section, the pulp was a dark brownish red, and a deep hemoglobin-stained fluid could be scraped off. The follicles and trabeculae were not visible.

The liver measured 19 by 15 by 5 cm. and weighed 965 Gm. The capsule was smooth. On section, the parenchyma was soft and dark brownish yellow. The acini were indistinct. The portal vessels were filled with a thick hemolyzed blood. The gallbladder contained a thick, dark orange-yellow bile. The mucosa was smooth and bile-stained.

The pancreas measured 11 by 2 by 1.5 cm. and weighed 38 Gm. It was firm, and on section the parenchyma was slightly hemoglobin-stained.

The right suprarenal capsule measured 3.5 cm. by 17 by 4 mm. and weighed 2.18 Gm. The left suprarenal capsule measured 3 cm. by 16 by 3 mm. and weighed 2.62 Gm. On section, the cortex was thin and pale yellow. The medullary substance was very scant and a brownish red.

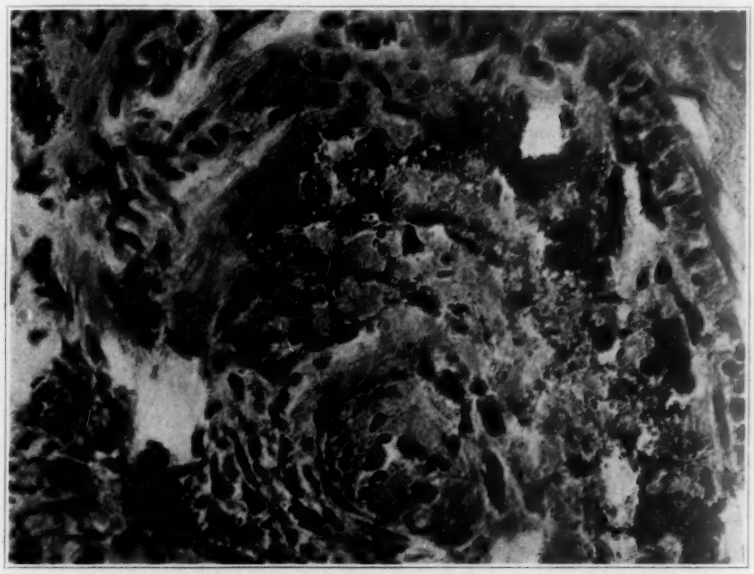

Fig. 4.—Section of the submucosa of the rectum, showing a medium sized artery surrounded by a few histiocytes and colonies of bacilli. There was no cellular reaction. Giemsa stain.

The right kidney measured 10 by 5 by 3.5 cm. and weighed 93 Gm. The left kidney measured 9 by 4 by 2 cm. and weighed 90 Gm. Both kidneys were embedded in a small amount of yellowish fat tissue. Both ureters were dilated to about the size of a lead pencil and filled with clear urine. The capsules were easily stripped off. The cortex was smooth and a light brownish yellow. On section, the cortical substance was slightly bulging, of normal thickness, showing a few reddish striations. The medullary substance was indistinctly outlined toward the cortex. The papillae were pale yellowish gray. The mucosa of the pelvis was smooth and stained a light yellow.

The peritoneal covering of the bladder was greatly edematous. On removal of the bladder, prostate and rectum, it was found that the rectum and the base of the bladder were surrounded by a thick mass of yellowish-gray, necrotic, friable, fibrin-like material. When the lumen of the bladder was opened, it was found to

contain about 50 cc. of a cloudy yellowish urine. The mucosa was greatly edematous, parts of it protruding into the lumen of the bladder in the form of gelatinous nodules. The orifices of both ureters were completely covered by the edematous mucosa.

The prostate and testes were without change macroscopically.

The stomach was distended. When it was opened, it was found to contain some coffee brown material mixed with mucus. The mucosa was folded, was a dirty grayish yellow and showed numerous punctiform hemorrhages. The duodenum contained some bile-stained material, and the mucosa was smooth and grayish white. The jejunum and ileum contained some soft smeary fecal matter. The mucosa was smooth and a pale grayish yellow. Peyer's patches were not enlarged. The appendix was of normal appearance; its lumen was filled with soft fecal matter. The entire colon contained a soft yellowish fecal matter; its mucosa was slate gray.

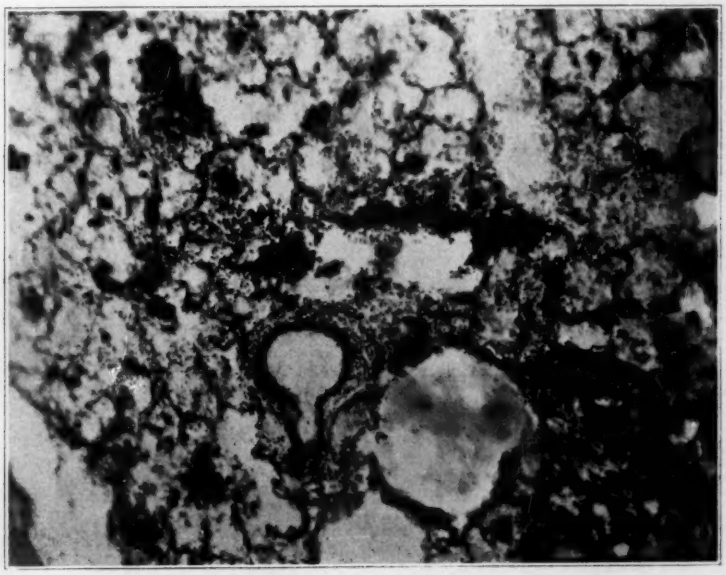

Fig. 5.—Section of the lung, showing alveoli filled with colonies of micro-organisms without cellular reaction. Celestin blue-eosin stain.

When the rectum was opened, the mucosa around the anus showed numerous confluent hemorrhages and was markedly edematous. There was a sharply outlined ulcer about 0.5 cm. in diameter, about 5 cm. from the anal orifice, without inflammatory reaction. The ulcer could be scraped off easily, and the underlying structures were transformed into soft, friable, necrotic, dirty yellowish material.

The bone marrow of the femur was a light grayish red.

Bacteriologic Observations.—Cultures from the blood and spleen showed Bacillus aerogenes-capsulatus (Welch). Cultures from the rectal abscess showed colon bacilli, staphylococci and Bacillus aerogenes-capsulatus (Welch).

Anatomic Diagnosis.—The diagnosis was: ulcer of the rectum; necrotic periproctitis; necrosis of the subperitoneal tissue of the small pelvis; edema of the mucosa of the bladder; hydro-ureter; parenchymatous degeneration of the myo-

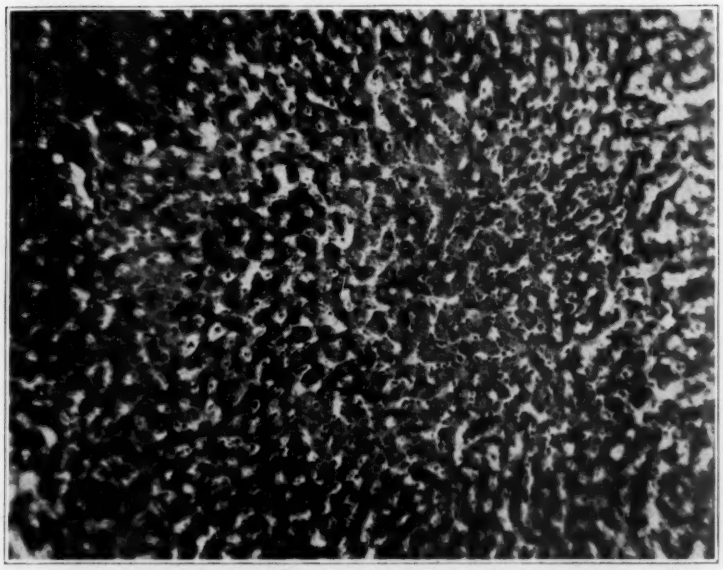

Fig. 6.—Section from the liver, showing focal necrosis. Celestin blue-eosin stain.

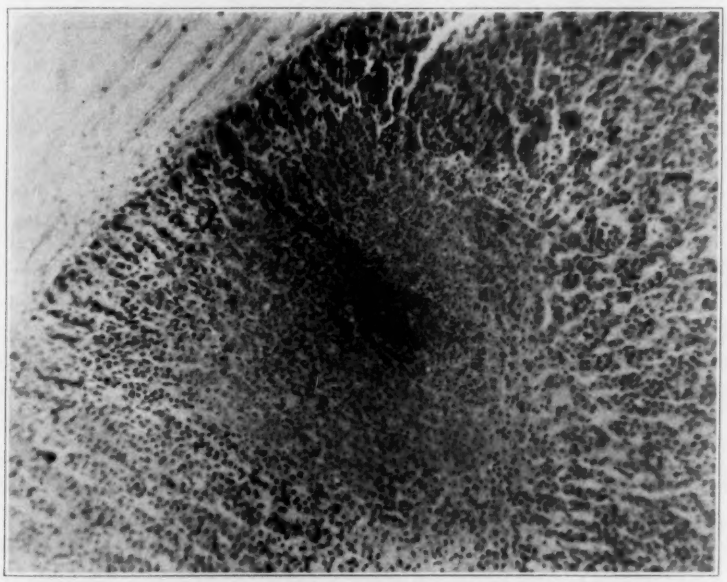

Fig. 7.—Section from the suprarenal capsule, showing focal necrosis. Celestin blue-eosin stain.

cardium, liver and kidneys; moderate bronchial pneumonia of both upper lobes and congestion of both lower lobes of the lungs; hemothorax; hemorrhagic ascites; hemorrhagic gastritis; splenitis; hemoglobinemia; moderate jaundice; lymphoid bone marrow.

Microscopic Observations.—Myocardium: The epicardium and myocardium were moderately infiltrated with lymphocytic elements. The vessels were partially or completely filled with fibrin, containing a few lymphocytic elements here and there. The muscle fibers showed fragmentations throughout. Striations were indistinct.

Lungs: The majority of the alveoli were filled with a homogeneous, reddish stained exudate mixed with either exfoliated epithelial cells or a network of fibrin. Enclosed in the exudate were colonies of micro-organisms containing myriads of

Fig. 8.—Section from the bone marrow, showing focal necrosis. Giemsa stain.

cocci and bacilli. No polymorphonuclear leukocytes could be found, only a few lymphocytic elements and histiocytes. The epithelial cells contained numerous granules of amorphous brownish pigment. The medium-sized veins and arteries were filled with a network of fibrin, and some of them contained colonies of micro-organisms. The oxydase reaction was negative.

Kidneys: The capillaries of the glomeruli were distended with endothelial cells. The capsular space was filled with fibrin, a few red cells and desquamated epithelium. There were small collections of lymphocytes here and there. The epithelial cells of the tubuli contorti were greatly swollen; their lumina were filled with a fibrin reticulum. In other places, the epithelium was completely necrotic and transformed into a coarse granular material. The epithelial cells of Henle's loops were swollen; their lumina were filled with exfoliated epithelial cells. Occasionally the collecting tubules contained a homogeneous reddish stained material.

Suprarenal Capsule: Throughout the cortex were numerous small necrotic areas; some contained colonies of bacilli. The lipoid content of the cortex was greatly reduced.

Liver: Focal necrosis was found throughout the liver parenchyma around the central veins. Some of the necrotic areas were surrounded with a few lymphocytes and contained numerous colonies of bacilli. The necrotic areas consisted of homogeneous, pale red-stained liver cells without an inflammatory reaction. The sinusoids were filled with fibrin. Where the liver cells were of normal appearance, the sinusoids were filled with red cells and a few phagocytes containing red cells or an amorphous brownish pigment.

Spleen: There was a marked congestion. The majority of the lymph follicles were small with indistinct germinative centers. The trabeculae were small and

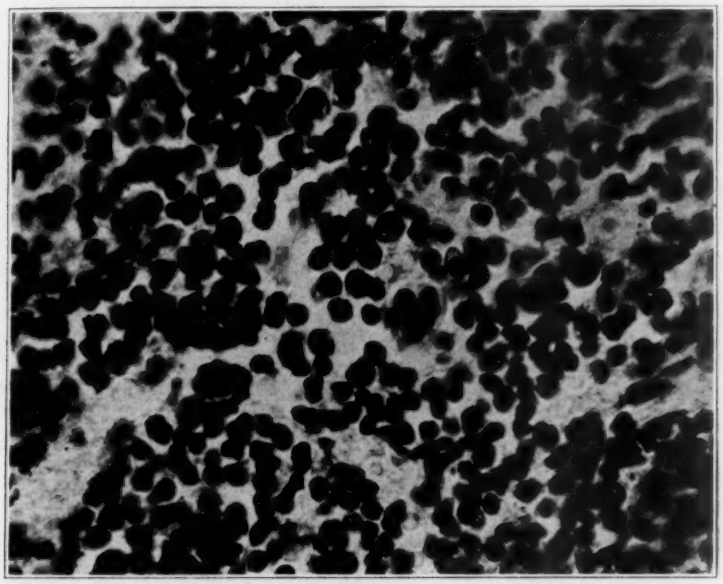

Fig. 9.—Section from the bone marrow, showing lymphadenoid hyperplasia. Megakaryocytes are seen. Giemsa stain.

indistinctly stained. The reticular tissue of the pulp was almost devoid of lymphocytes, but contained large numbers of red cells. The sinuses and splenic veins contained red blood cells, lymphocytes and large mononuclear phagocytic cells. Some of the latter were filled with disintegrated red cells, while others contained an amorphous brownish pigment. The oxydase reaction was negative.

Rectum: The mucosa around the ulcer was well preserved and without inflammatory reaction. The submucosa and muscularis were greatly edematous and broken up; the detached pieces of the muscularis were completely necrotic. The serosa was faintly outlined and was covered with a thick layer of fibrin and myriads of bacilli. There was only a slight lymphocytic-histiocytic reaction. Some of the histiocytes had phagocytosed a few bacilli. The oxydase reaction was completely negative. The walls of the blood vessels were completely necrotic and filled with

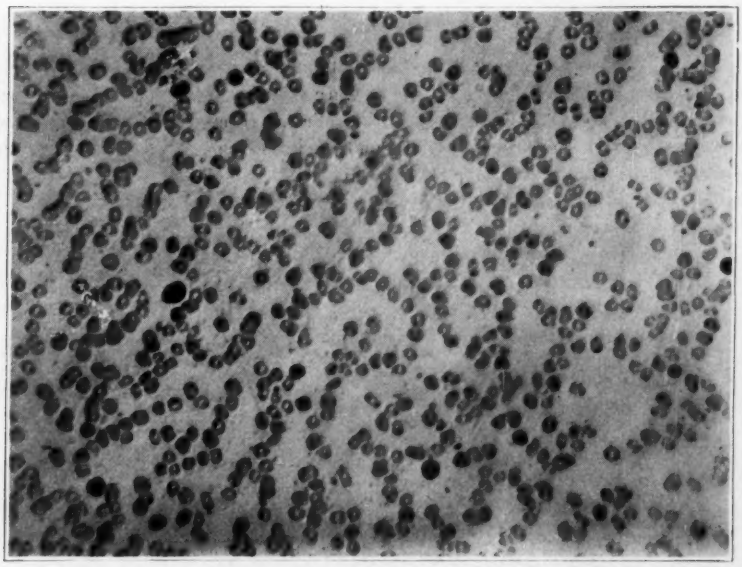

Fig. 10.—Photomicrograph of the heart blood, post mortem, showing lymphocytes only.

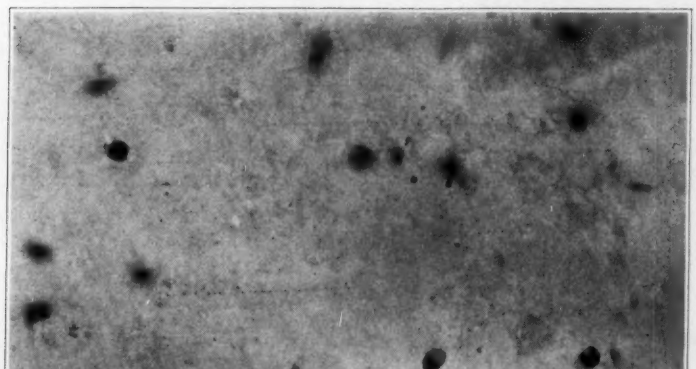

Fig. 11.—Section of the bone marrow of the femur and focal necrosis, showing a few monocytes.

either hyaline or fibrin thrombi. There was no inflammatory reaction around the blood vessels.

Bone Marrow: The granulocytes were completely replaced by lymphocytic elements. The oxydase reaction was negative. There were very few erythrocytes and nucleated red cells. The megakaryocytes were present in normal numbers. There were numerous large and small necrotic areas, and some contained large numbers of bacilli. The bacilli were also distributed throughout the lymphocytic cell masses, some of the capillaries being entirely filled with clumps of bacilli. The lymphocytes in the necrotic area were barely visible, but there were a few well stained cells of monocytic and histiocytic habitus. Many of the lymphocytic elements showed degenerative changes in the protoplasm and nuclei, especially around the border of the necrotic areas, where there were numerous vacuolated cells show-

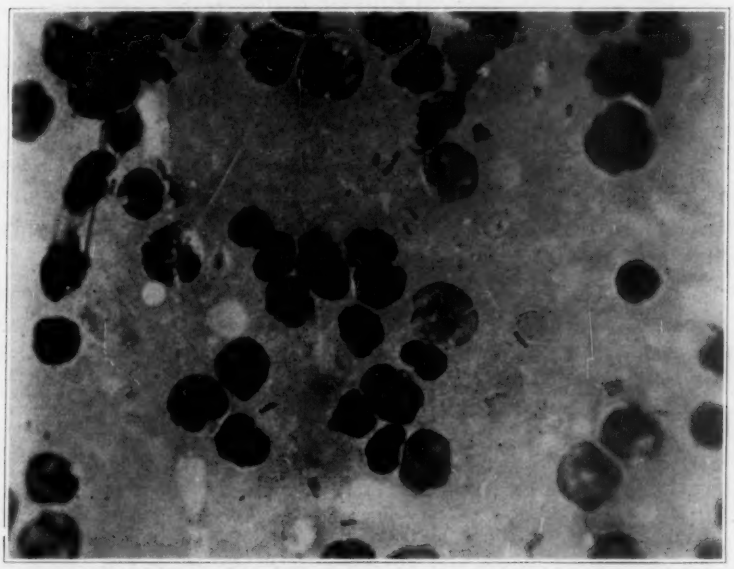

Fig. 12.—Smear of the bone marrow of the femur, showing degenerated lymphocytes, a few red cells and bacilli. Giemsa stain.

ing pyknosis and karyorrhexis of the nuclei and considerable granular chromatin detritus. Some of the megakaryocytes showed the same degenerative changes. The reticulo-endothelial elements were swollen, and some contained a crystalline or an amorphous brownish pigment.

Epicrisis.—The complete absence of the oxydase reaction, the lymphoid transformation of the bone marrow and the necroses found in the rectum, liver, suprarenal capsule and bone marrow are typical for agranulocytosis.

The infection with Bacillus aerogenes-capsulatus was of intestinal origin caused by the necrosis of the rectum with the formation of an extensive serofibrinous exudate extending to the floor of the small pelvis, involving the bladder and ureters.

The icterus sub finem vitae was probably caused by a combined effect due to the multiple necroses of the liver and the hemolysis through the toxins of Bacillus aerogenes-capsulatus.

COMMENT

Since Werner Schultz [4] (1922) described the disease that bears his name, there has been much discussion centered around the etiology of it and whether or not it should be considered as a disease *sui generis* and separated from already known diseases, such as sepsis with a lymphatic reaction, hemorrhagic aleukia or similar diseases. Schultz, Friedemann and a number of other authors are of the opinion that agranulocytosis is a specific primary disease of the hematopoietic system. Zadek,[5] David, Brochsitter,[6] Sternberg and others believe that agranulocytosis is only the manifestation of a constitutional reaction of the organism to any septic infection. Zadek is of the opinion that agranulocytosis is due to an individual abnormal reaction of the granulocytic apparatus.

The authors of the first group believe that the absence of hemorrhagic diathesis, thrombopenia and the normal condition of the erythropoietic apparatus is a definite sign that only the granulocytic apparatus is damaged by a specific noxa, and therefore the morbus Schultz is a disease *sui generis*. Zadek, Sternberg and the other authors of the second group emphasized the great similarity of the older cases of sepsis with a lymphatic reaction, hemorrhagic aleukia and acute lymphatic leukemia, and they considered the different disease pictures, caused by various noxae, as a manifestation of a changed reaction of the hematopoietic apparatus.

The pathologic changes are described by numerous authors, including Leon,[7] Rotter,[8] Bantz,[9] Petri,[10] Baltzer,[11] Leuchtenberger,[12] Zadek,[5]

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10. Petri, E.: Ueber schwere Veränderungen des gesamten Verdauungstractus bei der sogenannten Agranulocytose, Deutsche med. Wchnschr. **50**:1017 (July 25) 1924.

11. Baltzer, H.: Beitrag zur Kenntnis der Agranulocytosis, Virchows Arch. f. path. Anat. **262**:681, 1926.

12. Leuchtenberger, R.: Beitrag zur Frage der Agranulocytose, Folia haemat. **39**:63, 1929.

David, Kommerell [13] and others, but their findings vary considerably. The investigators who give an exact description of the bone marrow emphasize the almost or complete absence of granulocytes with a marked increase of the lymphocytic elements. In many cases only a macroscopic description is given. The bone marrow of the femur showed fat marrow only, or scattered islands of red marrow. David found normal bone marrow, and he thinks that there is only a disturbance in the emigration of the leukocytes. Rotter noticed the complete absence of myelocytes and found only a few myeloblasts. In his second case, he found degenerated myeloblasts besides numerous small lymphocytes, which formed small lymph follicles in many places. Leuchtenberger, in one of his cases, found lymph follicles in the marrow of the femur. Kommerell also described lymph follicles in the marrow of the femur. All mentioned authors found a large number of megakarocytes.

According to Oehme, Hedinger, Askanazy [14] and Hallermann,[15] the lymph follicles are not of pathologic significance, owing to the fact that they are found in the normal bone marrow and are not specific for agranulocytosis. However, Hallermann described one case of agranulocytosis that developed in connection with a long-standing rheumatic infection, in which the bone marrow showed a large number of lymph follicles, and he believed that this explained the depression of the hematopoietic function of the bone marrow. He thought that the chronic irritation of the rheumatic infection caused a hyperplasia of the lymphatic elements with a subsequent damage of the granulocytic apparatus. He found no increase in the lymphocytes in the blood stream and no other hyperplasia in the lymphatic apparatus of the body.

A large number of the agranulocytoses do not fit, *senso stricto,* into the disease picture first described by Schultz in 1922. The latter strictly distinguished between genuine and symptomatic forms. The dividing line between cryptogenetic and symptomatic is arbitrary, depending on the personal opinion of the author. Lubarsch's [16] dictum that pernicious anemia is a symptom complex that has to be solved etiologically also applies to agranulocytosis and aleukia.

Until there are more complete data on the etiology of agranulocytosis, the tentative classification of the hemocytotoxicoses by Bock

13. Kommerell, B.: Ein Beitrag zur Klinik der Agranulocytose, Med. Klin. **47**:1816, 1929.

14. Askanazy, M.: Knochenmark, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 1, pt. 2.

15. Hallermann, W.: Ein Beitrag zur Frage der Agranulocytose, Folia haemat. **42**:1, 1930.

16. Lubarsch, O.: Milz, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 1, pt. 2.

and Wiede [17] may serve for a differential diagnosis of the disease in question from a pathogenic standpoint. Their classification is based on the clinical blood picture, and, owing to the fact that some of the diseases in question may have a favorable outcome, they proposed the collective name of hemocytotoxicosis instead of hemophthisis. There is no doubt that some of the blood pictures are due to a temporary inhibition or a decreased cell emigration in the blood-forming organs without permanent pathologic changes. A rational nomenclature will tend to a better understanding of the different forms of the hemocytotoxicoses; for example: aleukia (damage of all white cells); agranulocytosis (damage of the granulocytes); alymphocytosis (damage of the lymphocytes). The following classification is suggested: erythrotoxicosis (aplastic anemia); megakaryotoxicosis (arthrombia); granulotoxicosis (agranulocytosis); leukotoxicosis (aleukia); panmyelotoxicosis (amyelia); universal hemocytotoxicosis (acythemia). The blood picture of these diseases is designated with the prefix a, while the word toxicosis is placed after the mother cell of the respective cell class. The name phthisis is reserved for only chronic symptomatic cases.

Animal experiments with known specific hemotoxic agents, which primarily affect the bone marrow, have so far been unsuccessful in producing the same form of hemocytotoxicosis in all individuals of the same species. The experiments with benzene demonstrate clearly that the produced blood pictures, thrombopenia, agranulocytosis, aleukia and myelopenia, are only varieties of a general hemocytotoxicosis, and that the susceptibility of a particular variety of blood cell in one individual may be much greater or less than the susceptibility of the same type of cell in another individual of the same species. The pathologic findings in arsphenamine poisoning also support this view. The difference in the histologic reaction is not influenced by the intensity and duration of the toxicosis alone, but probably depends, to a certain degree, on constitutional factors. Whether or not the sex factor plays a rôle is not known. Hemotoxins with a generalized action usually damage the granulocytes first and then the mother cells of the blood platelets. The erythrocytes and lymphocytic elements are the most resistant. Some hemotoxins have an intravascular action in addition to a central one. In the latter case, the blood platelets are the most susceptible.

Observations on human hemocytotoxicoses with known poisons show the same irregularities. One also sees a special affinity for certain cell forms, but these vary according to individual and constitutional factors. Known chemicotoxic and bacteriotoxic (sepsis) hemocytotoxicoses are classified under the symptomatic hemocytotoxicoses.

17. Bock, H. E., and Wiede, K.: Ueber Agranulocytose, Aleukie, Amyelhaemie und andere Hemocytotoxicosen, Folia haemat. **42**:7, 1930.

Complete and incomplete amyelia may be caused mechanically by a hyperplasia of other cell classes (lymphatic and monocytic leukemia).

There is a possibility that besides the etiologically known symptomatic hemocytotoxicoses, a real idiopathic hemocytotoxicosis exists, but this has not as yet been proved. Morbus Werlhof (symptomatic agranulocytosis) may have to be strictly separated from morbus Schultz (idiopathic agranulocytosis); idiopathic, isolated granulopenia from leukopenia, and the latter one again from morbus Frank (panmyelophthisis, no regeneration of erythrocytes, leukocytes and thromboblasts). There is a possibility of a central idiopathic erythrophthisis (Kaznelson type). The proof of a definite separate idiopathic form must be explained by special clinical symptoms, but the proof is so far lacking. In the so-called idiopathic forms, the hemotoxicosis is due to a primary damage of the premature cells, which progressively advances on the older cells. This is proved by the fact that in aplastic anemia only quantitative blood changes are found in the blood stream. Frank also found this to be typically true for panmyelophthisis, and it likewise holds good for agranulocytosis and aleukia.

In the majority of the symptomatic forms, the noxa attacks the bone marrow, but somewhat more peripherally. The normal myelopoiesis is inhibited, but in a centripetal direction; the normal emigration is blocked, and premature cells are often found. It may be that an individual allergy is necessary, since a pronounced eosinophilia is often observed. There may be a change in the normal reaction of the reticulo-endothelial apparatus (syphilis, malaria, polyarthritis, antisyphilitic treatment with heavy metals), or the noxious agent may be fixed on the cells of the blood-forming organs, as, for example, radium.

It is unlikely that the underlying cause is a primary weakness of the bone marrow. The observation of repeated attacks of the same disease in the same patient may be due to the constant presence of a specific attenuated infection (caries of the teeth). In a case of recurrent attacks of agranulocytosis over a period of ten years reported by Rutledge, Hansen-Pruss and Thayer,[18] the treatment for the chronic infection of the gums was the only thing that seemed to cause some improvement. The observation, in some cases, of an absolutely normal reaction to other acute infections also supports this view. Endocrine changes may play a rôle, but are less important. Further investigation is needed to elucidate other unknown etiologic causes. Our present experience with chemicotoxic hemotoxicoses points more to a toxin than to an organized noxa.

18. Rutledge, B. H.; Hansen-Pruss, O. C., and Thayer, W. S.: Recurrent Agranulocytosis, Bull. Johns Hopkins Hosp. **46**:369, 1930.

The separation of secondary from pathognomonic symptoms is important to clarify the various diseases according to types. As soon as the granular defense apparatus is defective, necrosis may appear, and this paves the way for septic secondary infections.

Toxic damages of the capillaries, hemorrhages, anemia caused by hemolytic micro-organisms, diminution of platelets, hemocytotoxicosis, icterus and enlargement of the spleen may be secondary symptoms. The type of cell regeneration of the secondarily damaged cells helps in separating the different types.

There is a close relationship between granulopenia and necrosis. It is found especially on mucous membranes that are prone to mechanical irritation (the pharynx, mouth, lower part of the rectum, genitals, entire gastro-intestinal tract, respiratory passages), but may also appear on the hands, breasts and ear lobes. Besides mechanical factors, the excretion of certain metallic poisons (bismuth and arsphenamine) through the mucous membranes of the pharynx and mouth is of importance.

The necrosis of the organs is primarily toxic and secondarily septic. Necrosis of the liver may cause icterus. It is of interest that other organs, especially those of the reticulo-endothelial apparatus, are the seat of necrosis in addition to the liver, spleen and bone marrow. This is in accordance with our opinion that the metabolic condition of the reticulo-endothelial apparatus is of some importance. If the reticulo-endothelial apparatus is already damaged to a certain extent by toxins, the formation of blood cells will be impaired. We do not believe that certain organs show a predisposition to necrosis.

There are no other cells that can fully replace the granulocytes as defense cells, at least in man and mammals. The phagocytic action of other types of leukocytes has been shown to be much less pronounced by Sabin.[19] Fibrin formation and hyalinization are unable to stop necrosis. The tissue monocytes that exhibit a slight phagocytic activity may replace the granulocytes to some extent, but they react very sluggishly to prevent necrosis and bacteremia. Cases with a marked monocytosis have a better immediate prognosis. In some cases plasma cells are found in large numbers at the place of infection, but their kinetic defense action is practically nil. The same is true for the lymphocytes, which, in spite of their marked increase in the blood-forming organs, are unable to change the course and prognosis of the disease. Bock and Wiede [17] found numerous toxic degenerated forms in cases of Schultz' agranulocytosis, which showed a marked diminution of the lymphocytes. They showed degenerative changes in either the cytoplasm or the nuclei

19. Sabin, E. R.: Studies of Living Human Blood Cells, Bull. Johns Hopkins Hosp. **34**:277, 1923.

(vacuolization, clumping of azurphile granules, pyknosis of the nuclei). They were unable to decide whether the degenerative changes were peripheral or central. If the latter could be demonstrated definitely, it might be of value in differentiating between lymphatic leukemia and agranulocytosis.

Agranulocytosis is a disease *sui generis* and should not be considered as a lymphatic reaction. In general, the disease picture in the majority of published cases follows the description given by Schultz.[4] In only a few cases have there been unimportant deviations from the classic course, and these need not be considered seriously. Our case showed the same classic symptom complex, but was, *sub finem vitae*, complicated with a marked decrease in the erythrocytes and hemoglobin. According to the foregoing classification, it would be intermediary between an agranulocytosis and a panmyelophthisis. Such variable blood pictures are observed in benzene and radium hemocytotoxicoses in which an athrombia may change into an agranulocytosis and further into an amyelemia or acythemia. We may therefore expect that such secondary changes may occur in cases of essential hemocytotoxicoses. A definite differentiation between an essential and a symptomatic agranulocytosis is difficult, since the etiology is obscure and the after-effects of other diseases, syphilis, for example, have to be considered. In his latest publication, Schultz [4] discussed this question at length and expressed the belief that the agranulocytosis of the adolescent is, in the majority of cases, symptomatic.

Schultz [4] and Leon [7] called attention to the fact that in most cases severe dental disease had existed for some time before the agranulocytosis manifested itself, or that it followed dental treatment. However, there is no proof that the granulocytopenia did not exist before the dental infection. Bock and Wiede [17] noticed this connection in a large number of cases of acute leukemia, and further observation will be necessary to establish the connection between chronic septic dental conditions and agranulocytosis. There is a possibility that in long-standing cases of septic oral conditions the leukopoiesis may be damaged by bacterial toxins. In view of the great prevalence of oral sepsis, the incidence of agranulocytosis is relatively small. Therefore, other unknown factors or certain constitutional conditions must be considered.

Septic processes of the tonsils play no rôle. The necrosis is merely a manifestation of the disease.

The clinical differentiation of acute lymphadenosis and aleukemic leukemia from agranulocytosis is often difficult. The microscopic examination of the bone marrow allows, in most cases, a definite anatomic separation of both diseases. The differentiation from sepsis is less difficult. Without doubt there may be a pronounced neutropenia in

septic conditions, but one will always find myelocytes in such cases. We agree with Friedemann [20] that sepsis should be diagnosed only when definitely known micro-organisms can be demonstrated in the blood stream; otherwise, every infectious disease would be diagnosed as sepsis. The main argument against sepsis is the absence of fever at the time when the granulocytes are disappearing from the peripheral blood. Cases without any fever have been observed by Bock and Wiede [17] and Reye.[21] The micro-organisms found in cases of genuine agranulocytosis are merely secondary infections due to the necrosis. We therefore consider genuine agranulocytosis as a definite clinical entity caused by a myelotropic agent and characterized by a pronounced granulopenia and necrosis formation. Pathogenically and morphologically, there is a close connection between agranulocytosis and hemocytotoxicoses in general.

The most important differential diagnostic clinical sign is the absence of hemorrhagic diathesis. The exact definition of the latter is rather difficult. Isolated hemorrhages, as we notice them in a number of various pathologic conditions without thrombopenia, cannot be considered as a hemorrhagic diathesis *sui generis*. Thrombopenia explains only the inability to arrest a hemorrhage. There must still be another factor, a lesion (traumatic, toxic, infectious, nervous or constitutional) of the vessel wall. In the course of agranulocytosis one may see hemorrhages that are probably caused by secondary infection. Only extensive hemorrhages with a marked diminution of the bleeding and clotting time may speak against agranulocytosis. It is important that the blood platelets in agranulocytosis are not diminished, and in spite of intravascular destruction, due to secondary infection, remain normal, or nearly normal, because the megakaryocytes in the bone marrow are not damaged. Whether or not the fatty degeneration of the capillary endothelial cells explains the hemorrhages, as found in the cases of Bock and Wiede, remains to be seen. Fatty degeneration is observed in a great number of infectious diseases without hemorrhages. Zadek [5] observed a case of agranulocytosis combined with hemorrhagic diathesis in which the blood platelets numbered 950,000.

Another much debated symptom in agranulocytosis is the icterus. Some authors regard icterus as a symptom of sepsis, while others regard it as unimportant. Friedemann [20] observed icterus only once in twenty-nine cases. Bock and Wiede [17] saw a slight icterus in three cases. The icterus is either pleiochromic or hepatotoxic. In cases of hemocytotoxicosis, i. e., in agranulocytosis and amyelemia, the icterus is of a

20. Friedemann, U.: Angina agranulocytica, Ztschr. f. klin. Med. **108**:54 (May 21) 1928.

21. Reye, A.: Zur Frage der Agranulocytose, Med. Klin. **7**:257, 1929.

hepatotoxic nature. In no case is the liver normal; cloudy swelling and fatty degeneration are always present. Bock and Wiede described the first case in which a few scattered single cell necroses were found. In our case we found central necrosis and single cell necrosis throughout the liver parenchyma. Krjukow [22] found necrosis in a case of acute lymphatic leukemia. Schaefer [23] and Baltzer [11] reported small localized massive necroses. Whether or not the necrosis explains the icterus remains to be seen. The origin of the necrosis, if bacterial or toxic and if pathognomonic for agranulocytosis or for the hemocytotoxicoses in general, is still a debated question. Bock and Wiede are inclined to believe that the necrosis is caused by bacterial toxin similar to the necrosis in diphtheria and in sepsis. There is a possibility that other factors contribute to the icterus besides the necrosis. Perhaps the destruction of the red cells as such or a change in the normal catabolism, set free by the destroyed red cells or a combination of both, is the aggravating factor. The morphologic blood examination alone cannot decide this question. Quantitative determinations of the excretion of urobilin are necessary to settle the question of an increased blood destruction. So far, quantitative determinations of urobilin have not been made in the cases of agranulocytosis published. At present we agree with Bock and Wiede, that the icterus in agranulocytosis is essentially a hepatotoxic icterus that may be greatly accentuated by an increased erythrolysis, but does not play an important rôle in the pathogenesis of the hemorrhages.

Enlargement of the spleen has no pathognomonic significance in agranulocytosis and is due to a secondary infection.

The relationship of the lymphocytic and monocytic reaction to hemocytotoxicosis is of great importance from a differential diagnostic standpoint. We may speak of a lymphatic reaction when an absolute increase of the lymphocytes is found; the same applies to the monocytic reaction. Sometimes a lymphocytic monocytic reaction is found when both cell types are absolutely increased. The main defense reaction against acute infection is performed by the myeloid cells, especially by the segmented neutrophil granulocytes. A person can exist without lymphocytes and monocytes, but not without granulocytes. The question arises as to the significance of the lymphocytic reaction in cases of agranulocytosis. According to the experiments of Kauffmann, the lymphocytes are not defense cells in acute inflammatory reaction. In four cases of lymphatic leukemia, he found only neutrophil granulocytes

22. Krjukow, A.: Ueber die myeloblastischen Plasmomyelome, Folia haemat. **17**:75, 1914.

23. Schaefer, R.: Zur differential Diagnose der Agranulocytose, Deutsches Arch. f. klin. Med. **151**:191 (Dec. 18) 1926.

in the artificial blister exudate. From these observations it is evident that the lymphocytes in agranulocytosis cannot replace the granulocytes, and therefore the lymphatic reaction is very likely a constitutional one, or may be due to the unknown noxa. Naegeli expressed the belief that the lymphatic and monocytic reactions are caused by a special peculiarity of the infectious micro-organisms. He quoted Sternberg and Marchand, who believe that the streptococcus in its various biologic varieties, may cause a myelocytosis in one case and a lymphatic or monocytic reaction in others. The difficulty lies in the ignorance concerning the biologic changes or mutations of known pathogenic micro-organisms. On the other hand, the toxic products formed by chronically infected teeth or tonsils may cause a change in the cellular defense. The combination of agranulocytosis with a lymphocytic and monocytic reaction undoubtedly speaks for a close relationship of the underlying cause. If the lymphocytic reaction in agranulocytosis is really a defense reaction, one should expect an increase in the lymphocytes in the course of the disease, but such is not the case. As soon as necrosis sets in, there is a rapid decrease of the granulocytes together with a continuous decrease of the total leukocyte number. Similar conditions occur in agranulocytosis with a monocytic reaction without damage to the monocytes. The prognosis in cases of agranulocytosis with a monocytic reaction is not so hopeless, as the monocytes are capable of phagocytic action. Regardless of the marked increase in monocytes, they never can fully replace the granulocytes in preventing necrosis.

The cause of necrosis is undoubtedly the great numerical reduction of the granulocytes. This view is supported by the observations of Frank [24] in cases of panmyelophthisis. Only the cases with high granulocyte counts showed no necroses. Further proof of this has been observed in cases of lymphatic leukemia with an agranulocytic symptom complex. Askanazy [14] has undoubtedly shown that necroses in leukemia are mainly due to the destruction of the leukemic infiltrations, but as Bock and Wiede [17] have found necroses in places without infiltration, the cause must be due to a deficiency of the granulocytes. Schultz [4] advanced the hypothesis that a hormonal deficiency probably plays a rôle, especially where the necroses cannot be caused by mechanical injury; for instance, in the suprarenal capsule, liver and tonsils. The critical granulocyte number below which necrosis is imminent is about 800 per cubic millimeter of blood. Since Reye [21] and Kommerell [13] have observed cases with extremely low numbers of granulocytes without necroses, for several months, perhaps other factors besides the extreme leukopenia may play a rôle.

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24. Frank, A.: Aleucia haemorrhagica, in Handbuch der Erkrankungen des Blutes und der blutbildenen Organe, Berlin, Julius Springer, 1925, vol. 2.

There is nothing definitely known about the *modus operandi* of the regeneration of the granulocytes in agranulocytosis. In the few cases in which a regeneration or complete recovery took place, it seems that an increase was due to the adolescent forms of the polymorphonuclear granulocytes. Myelocytes were never observed in large numbers. It seems that the emigration of the granulocytes is blocked by some unknown cause. The destruction of the granulocytes in symptomatic hemocytotoxicosis in contrast to the genuine seems reversed. The unknown noxa first attacks the fully developed forms of the granulocytes and then ascends to the premature forms. The occasional finding of normal bone marrow in cases of fully developed peripheral hemocytotoxicoses seems to support this view.

The microscopic observations in the bone marrow vary according to the state in which the disease terminates. Sometimes, even in advanced cases, a few granulocytes may still be present. In uncomplicated cases the megakaryocytes are not damaged. An entirely cell-free bone marrow, as is seen in complete hemocytotoxicosis, is rarely found except in chronic symptomatic forms in which a differentiation between symptomatic and genuine cases is impossible. Toxic changes in the mononuclear cells (lymphocytes?) were described by Naegeli and Schilling as follows: "The damaged cells were large, fragile forms with pale stained nuclei and light blue, indistinctly stained, protoplasms while others either showed a dark blue or vacuolized protoplasm. The nuclei showed all forms of pyknosis and karyorrhexis. The azurophile granules were indistinctly stained and clumpy."

According to Bock and Wiede,[17] the plasma cells are not toxic lymphocytes, but are functional forms that may originate from myeloid as well as from reticulo-endothelial cells. Alterative changes were also observed in so-called atypical plasma cells with shrunken nuclei and more or less pronounced vacuolization of the protoplasm. Bock and Wiede found that cases with extremely low leukocyte counts showed the highest percentage of toxic lymphocytes. The damage of the lymphocytes was observed after the granulocytic changes. The lymphocytes seem to have a greater resistance than the granulocytes. No definite changes could be observed in the monocytes.

PROGNOSIS

From the blood findings, the following points are of prognostic value: Complete disappearance of the oxydase reaction of the granulocytes is a bad prognostic sign and reappearance a favorable one. The absence of eosinophils is without significance. If the granulocytes fall below 800 per cubic millimeter, the danger of necrosis is very great, and consequently the prognosis is unfavorable. An absolute increase

of the monocytes has been interpreted as a favorable sign. In the chart in our case (fig. 1) it will be noted that there was a rise of the monocyte count prior to each remission, but that there was also an increase in these cells during the last attack, which proved fatal. The emigration of oxydase-positive elements, after the injection of thyroxine, may be a favorable sign. The increase of the lymphocytic elements is of no significance. The provocation of a turpentine abscess is not only the most reliable prognostic procedure, but also of at least temporary therapeutic value. A continued increase of the segmented neutrophils assures a favorable outcome. (A typical remission was heralded by an increase in neutrophils, with some myelocytes, in our case.) The presence or spontaneous appearance of premature myeloid elements is favorable. So far all cases reported in children with the clinical course and picture described by Brennemann and Bigler have been fatal. They gave the duration of the disease as from two to five months. The known duration of granulocytopenia in our case is a little less than six months.

TREATMENT

Many types of treatment have been used for agranulocytosis in adults. Daily injections of nucleinic acid and its decompensation products have recently been reported as favorable by Gordon [25] and others.[26] In our case, leukocytic extract in large doses, a daily injection of nucleinic acid (5 per cent), stimulation of the long bones with small doses of the x-rays, injections of whole pituitary solution (Armour), autogenous vaccine, blood transfusions and oral hygiene with perborate mouth washes were used at different times. In addition, the patient was given one vial of liver extract and two dessertspoonfuls of cod liver oil daily, after August 14. He had received considerable heliotherapy between his first and second attack. The diet was purposely made low in fat. Of all the methods of treatment used, the blood transfusions alone seemed to be of demonstrable value. In the chart, it will be noted that the rising of the neutrophil count, which began on August 19 and again on September 12, followed three days after a blood transfusion in each case. Figure 1 also shows that there was no response to the last three blood transfusions, probably because the granulocytic function of the bone marrow had become nearly or completely exhausted by that time. It seems likely that the persistent

25. Gordon, W. H.: Agranulocytosis, Ann. Int. Med. **3**:1008 (April) 1930.

26. Reznikoff, Paul: J. Clin. Investigation **9**:555 (Feb. 20) 1931. Jackson, Henry, Jr.; Parker, Frederic, Jr.; Rinehart, J. F., and Taylor, F. H. L.: The Treatment of Malignant Neutropenia with Pentose Nucleotides, J. A. M. A. **97**: 1436 (Nov. 14) 1931.

use of the perborate of sodium mouth wash and gargle may have prevented a more virulent secondary infection in the mouth and throat. The interesting effect of nonspecific protein therapy was shown when the patient was given a very small dose of an autogenous staphylococcus vaccine on September 30. Two days later the lymphocyte count had doubled, but the neutrophils showed no increase, and the effect was quite transitory. It is possible that the beneficial effect of blood transfusions may be due to the same substance that is present in leukocytic extract, since Gray [27] has recently reported beneficial results with large doses of the latter. The leukocytes administered in the donor's blood are completely broken down, with a liberation of substances probably similar to those present in the extract obtained by extracting the white blood cells of slaughtered animals. The objection to leukocytic extract is the pain caused by the daily intramuscular injection of such huge doses as are apparently necessary. For this reason transfusions once or twice weekly would seem preferable unless the leukocytic extract could be given intravenously. In cases with secondary reduction of the erythrocytes, transfusions of blood serve an addition purpose in combating the anemia.

SUMMARY

1. A case of primary, idiopathic agranulocytosis in a child is reported.

2. A study of this case supports the view that the disease is caused by an unorganized noxious agent that acts on the bone marrow, for the following reasons: (*a*) No evidence of a focal infection could be demonstrated clinically previous to the time when the granulocyte count fell so low as seriously to impair the body's defense against saprophytic organisms. (*b*) The type of necrosis that was found pathologically. (*c*) A blood culture was negative during an afebrile remission of the disease, even though the granulocyte count was gradually falling.

3. The only noxious agent that we were able to find in this case was exposure to the fumes given off by the flue of a gas-burning furnace in the home for a period of at least three weeks. This exposure occurred more than twelve months prior to the appearance of the first symptoms attributable to the disease. A careful history in forthcoming cases, including thorough questioning regarding the possibility of exposure to some chemical poison, might throw more light on the etiology. Such questions as "What form of heating do you use in your home?" and "Have you ever had trouble with your electric refrigerator?" are not ordinarily asked in medical histories.

27. Gray, G. A.: Agranulocytic Angina, California & West. Med. **34**:402 (June) 1931.

4. Blood transfusion and oral hygiene were the only therapeutic measures that seemed to be of value.

5. All cases so far reported in children, with the general symptomatology and blood picture here described, have proved fatal in less than six months after the onset of the first symptoms. Symptomatic cases such as are occasionally found after a prolonged pyogenic infection or other chronic diseases have a better prognosis in children and should therefore be distinguished whenever possible from the type of case reported here. For the present, the latter may be called idiopathic or primary agranulocytosis, and the former can be considered as secondary.

Pediatric Biographies

CLAUDE QUILLET
1602-1661

JOHN RUHRÄH, M.D.
BALTIMORE

Claude Quillet was born at Chinon, in 1602; not a great deal is known about him, but the very name of his birth place calls up the picture of Jeanne d'Arc, singling out Charles VII from all his nobles and persuading him to hasten to the relief of Orléans. It recalls too another remarkable character, Rabelais, the merry vicar of Meudon, and a credit to the medical profession. Quillet studied medicine, gained a measure of success and then incurred the enmity of Richelieu and others powerful in political circles. He defended Urbain Grandier, the priest of Loudun, accused of witchcraft, of sending Astaroth to torment the inmates of an Ursaline convent in the town. Relatives of Sourdis and of the great Richelieu were among those dwelling in the nunnery. The trial, one of the most famous of the multitude of such cases, makes good reading—a chapter in human history almost as incomprehensible as our present prohibition. Despite the efforts of Quillet, Grandier was publicly burned at the stake. Not knowing what might happen next, the valiant defender fled into Italy, where he took holy orders and eventually became secretary to the French Ambassador, Maréchal d'Estrées. After Richelieu's death, Quillet returned to France and Cardinal Mazarin made him Abbé of Doudeauville, where, devoting himself to the pursuits of peace, he wrote under the pseudonym of Calvidius Letus, an anagram on his own name. His chief work is a poem in Latin, published at Leyden in 1655, entitled "Callipaedia seu de Pulchrae Prolis Habendae Ratione," or "The Way to Have Handsome Children." It was a popular poem and went through several editions, and was translated many times into French by Monthénans, 1749; Lancelin de Laval, 1774; Caillau, 1799, and Comas Doran, 1832. There is an anonymous translation into English, dated London, 1710; the same volume contains the "Paedotrophia" by Sainte-Marthe.

The translations of the poems are dedicated to Dr. Garth. Among other things the dedication says:

Whether his and St. Marthe's *knowledge of* Physick *and* Medicine *be Just and Considerable, I leave to you, Sir and the Gentlemen of the* College, *to determine; if I have done my Authors any Injury therein I cou'd not help it. You are your selves in some wise to blame, since, if you had undertaken to make 'em* English, *none of us wou'd have dar'd to have attempted it: And if you, Sir, especially had*

CL. QVILLETI

CALLIPAEDIA,

SEV

DE PVLCHRAE PROLIS
HABENDAE RATIONE,

POEMA DIDACTICON.

CVM VNO ET ALTERO
EIVSDEM AVTORIS CARMINE.

IVXTA EXEMPLAR EXCVSVM.

PARISIIS,
Apud THOMAM JOLY.

M. DCC. IX.

Title page of "Callipaedia."

had Leisure and Disposition to have done it, my Originals *wou'd have had little more than the Merit of imperfect* Copies; *so much greater is your* Mastery *in one* Art, *and your* Genius *in the other.*

The poem starts out with an invocation, the opening lines of which are:

I sing the Pleasures of the Nuptial Bed,
And the fair Product of the Genial Seed,
What Skies, propitious to the dear Embrace,
Imprint their Brightness on a beauteous Face;
How, in one happy Object, we may find
A charming Body with a lovely Mind;
How the glad Parents, when the Boy is born,
With shining Virtues may his Soul adorn.

The poem is good reading. It pictures a nymph of marvellous perfection made by Jove especially for men. It thunders against the transmission of hereditary diseases, of infections, and there are comments on the young mating with the aged. The very young are not to wed; a girl should be 12 before she thinks of it. In the second book rules are given on how to create fine children, and the effect of food, drink and the stars; there are comments on the signs of the Zodiac and on anatomy and physiology. Quillet gives the hygiene of pregnancy, in an amusing way, and counsels against too much exertion and dancing and also against too much idleness. The last part of the book is given over to the education of the child. It is a sprightly book and an entertaining one.

According to Quillet, boys result from the use of properly selected wines, somewhat reversing Schenck and the old nursery rhyme to the effect that little boys are made of "snaps and snails and puppy dog tails." On this point he says:

Sufficient for the Nuptial Joy's the Vine,
And lusty Boys are got by gen'rous Wine.
But most, Oh *Burgundy!* thy Nectar warms
Their Hearts, and burnishes their Bridal Arms.
Both bright *Champagne* with equal Vigour fills,
And the rich Cluster of the *Aisian* Hills.
And you, ye Wives, who with your Husbands join,
To pray for Sons to prop an Ancient Line,
At Meals, with sparkling Wine rejoice your Souls,
And freely pledge 'em in their modest Bowls.

Against excess he warns, giving various dangers and ends.

Let Reason in your Cups direct your Draught
The Ship is often sunk when over fraught.

To consider the influence of the stars was the fashion of the time, and even today astrologers speak over the radio.

When the Ram rules, or when the Lion shines,
Or when the Ballance, Centaur, or the Twins,
Or when the Radiant Urn its Light displays,
A Boy expect to crown the close Embrace.
The rolling Planets are to Males inclin'd,
As in the Lessons of the Learn'd we find.
Thus *Saturn,* furious Mars, and Sov'reign *Jove,*
Reward with Boys the Parents faithful Love.

The effect of maternal impressions is commented on at some length:

Since by foul Objects filthy Births are made,
And the vile Picture's to the Womb convey'd,
A pregnant Wife will ne'er behold a Whale,
Nor Porpus, nor the Dolphin's Azure Scale.
Nor thee, Oh *Proteus,* will she see, nor you
Tritonian Monsters, while she's Teeming, view;
But let her on the lovely *Nereids* gaze,
And fix her Eyes on ev'ry charming Face.
Ye Pregnant Wives, whose Wish it is, and Care,
To bring your Issue, and to breed it Fair,
On what you look, on what you think, beware.
A Boy your Wish, a beauteous Boy behold,
With Lips a Cherry red, and Locks of Gold;
Like him for whom *Alexis* sigh'd of old.
Or in *Apollo's* Radiant Youth delight,
And like *Apollo,* shall the Birth be bright.
If Female Fruit you rather covet, view
A Heav'nly *Venus,* such as *Titian* drew.
Or beauteous *Danae,* when her Virgin Flow'r
By Jove was gather'd, in the Golden Show'r.
But if the Beauties of our Age can please,
Fair *Phyllis view;* for she's as Fair as these.

One more short quotation containing the old fallacy of the disposition of the child and the milk may be quoted:

We never can enough those Parents blame,
Who, careless of a Mother's sacred Name,
To Ign'rant Nurses their poor Infants trust;
To such, as neither will nor can be Just.
Oft at a Venal Pap they suck their Bane,
And in their Blood the Latent Plague retain.
But of those Evils not to speak, which flow
From the first Draughts, and with the Body grow;
The Mind's affected by corrupted Juice,
If bad the Milk, the Manners may be loose.
Who knows not that a Whore's malignant Pap
Corrupts the Infant, in her wanton Lap;
With Lust and impious Fires it fills his Breast,
And seldom is the Child, so suckled, Chast.

Pediatrics in Art

RICKETS

JOHN RUHRÄH, M.D.
BALTIMORE

Madonna with the Child and St. John

Botticelli, Sandro, or Alessandro di Mariano dei Filipepi (1444-1510), has contributed a number of things to pediatric art. His painting of the Virgin and the Child and St. John in the Dresden Gallery is a good example of rickets. Nearly all the bambinos of early Italian art show signs of this disease, from which one may infer that rickets was rather general at the time the pictures were painted. Here one sees the swellings of the wrists and ankles well marked.

News and Comment

GENERAL

Bequests and Donations.—The Child's Hospital, New York, received $10,000 from the will of Alice Shilleto.

St. Mary's Hospital for Children, New York, was bequeathed $5,000 by the will of Mrs. Harriette M. Dickinson.

New York Foundling, New York, was left $10,000 by the will of Giulia P. P. Morosini.

The Babies' Hospital, Philadelphia, was bequeathed $5,000 by the will of John F. Huneker.

Montgomery Hospital, Morristown, Pa., was given $50,000 to be used for a children's ward, by the will of John Hoffman, Jr.

Nervous Disease Hospital for Children in Long Island.—The Emma Pendelton Bradley Home was recently opened in East Providence. It is said to be the first hospital for children under 13 years of age who are suffering from nervous and mental disorders.

Children's Clinic of the Faculty of Medicine of Strasbourg.—An advanced course in pediatrics will be offered at the Children's Clinic of Strasbourg, October 10 to 22 under the direction of Professor Rohmer. The lessons will deal with alimentary hygiene and diseases of infancy (normal feeding, digestive disturbances, dystrophies, infectious diseases, etc.), as well as with pediatric problems of the day. A detailed program will be published later.

Pediatrician on Executive Committee, National Board.—The readers of the AMERICAN JOURNAL OF DISEASES OF CHILDREN will be more than pleased to know that at last there has been a pediatrician appointed on the Executive Committee of the National Board of Medical Examiners. As a representative of the Association of American Medical Colleges, Dr. A. Graeme Mitchell, professor of pediatrics in the University of Cincinnati College of Medicine, was unanimously elected to membership on the Executive Committee of the National Board of Medical Examiners. This is a step forward not only for pediatrics, but also for the National Board.

Obituaries

A. D. BLACKADER, M.D.

1847-1932

Dr. Alexander Dougall Blackader, M.A., M.D., C.M., LL.D., died at his home in Montreal on March 14, 1932, after a week's acute illness, though he had been in failing health for several years. He was one of the best known figures in the American medical fraternity, and his reputation as a pediatrician, physician and editor extended over the whole English-speaking world.

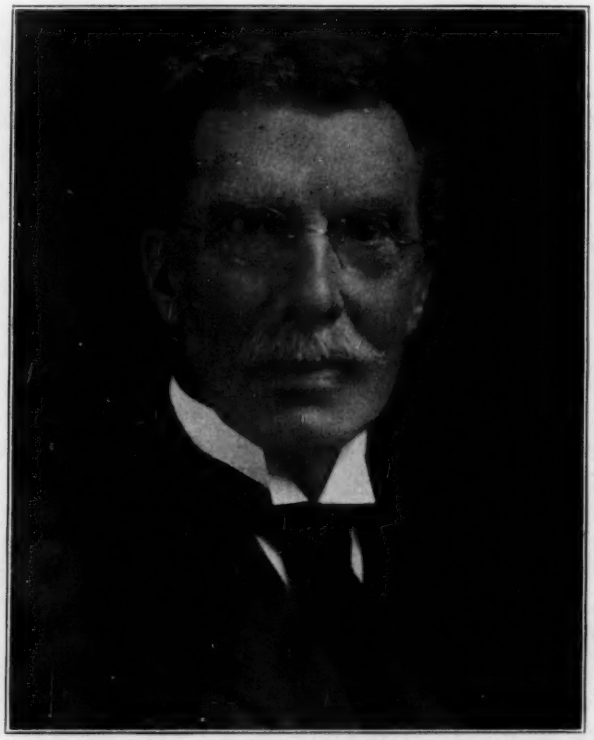
Dr. Blackader was born in Montreal in 1847, graduated from McGill Medical College in 1871, served his apprenticeship as intern in the great Ormond Street Hospital for Sick Children in London and spent his life in the practice of medicine in Montreal. An able speaker and writer, intensely interested in all work connected with child welfare and public health, his reputation as a child specialist soon spread beyond the borders of his native land. He was a pioneer in the specialty of pediatrics in Canada, and it was largely through his efforts that the importance of the subject in medical education became recognized in Canadian universities. He was one of the original members of the American Pediatric Society, later its president and afterward an honorary member.

His charming manners, old-world courtesy and boundless hospitality endeared him to all his associates and made him a familiar figure in all medical assemblies. His friendships were world-wide, and many will miss him.

Dr. Blackader was a man of extraordinary industry, and though busy all his life with a large family practice, he found time to make a name for himself in many fields, apart from his chosen specialty of pediatrics. A skilled pharmacist, he was for many years professor of pharmacology and therapeutics at McGill University. Interested in all that pertained to therapeutics, he became an ardent member and eventually president of the American Climatological Society.

After reaching the age of 70 years, although in impaired health, he accepted the editorship of the *Canadian Medical Association Journal*. It was largely due to his efforts that this magazine was brought to a state of excellence that made it one of the best journals of its kind in the British Empire.

Few men have acquired so great a reputation in so many different fields of activity. As editor, professor, pediatrician, therapeutist, climatologist and pharmacist, he was widely known. But it was as personal friend and family physician that he was most beloved, and few families in his native city of Montreal were not indebted to him for kindly services and help in time of distress.



A. D. BLACKADER
1847-1932

With his declining years most of the honors of the medical world were bestowed on him. He was made honorary member of the British Pediatric Society, LL.D. of McGill University and vice president of the British Medical Association, and was given many other honorary positions.

Nowhere will his loss be more felt than in his native city, where he devoted the greater part of his life to educating the public in the care of children and the prevention of disease.

H. B. C.

STAFFORD McLEAN, M.D.

1886-1932

After an active day of work in his office and at the hospital, March 12, 1932, Dr. Stafford McLean retired in apparently good health. He was found the next morning dead from sudden cardiac failure. This was the untimely end of a comparatively young and outstanding pediatrician who was only beginning to reap the higher rewards of years of observation and study of children and their diseases.

Dr. McLean was born at Newburgh, N. Y., in October, 1886, and is survived by his widow, Elizabeth Cutting McLean. He studied at Georgetown and at Columbia University, graduating in medicine at Columbia in the class of 1908. His first eighteen months after graduation were spent as intern in the First Medical Division of Bellevue Hospital, New York City. His career in pediatrics was then begun with a service under Dr. John Howland, chief of the Children's Medical Service of Bellevue Hospital. He devoted the next two years to study in Germany under Arthur Keller and Leo Langstein as resident physician to the Kaiserin Augusta Victoria Haus, Berlin.

On his return to America in 1912, he came under the leadership of Dr. L. Emmett Holt at the Babies' Hospital and entered the private practice of pediatrics in New York City. The life and achievements of Dr. McLean are closely interwoven with the development of the Babies' Hospital and the Medical School of Columbia University. He gave twenty years of faithful service to these institutions, and at the time of his death was a senior attending physician and secretary of the medical board of the Babies' Hospital and clinical professor of diseases of children on the faculty of the university. He was also attending pediatrist of the New York Orthopedic Hospital and consultant pediatrician to the Tuxedo Memorial Hospital, Tuxedo, N. Y., and the Horton Memorial Hospital, Middletown, Conn. He was active in the affairs of the New York Academy of Medicine, having served as both secretary and chairman of the Pediatric Section. In 1916, he became a director of the Children's Welfare Federation of New York City and served as chairman of the Committee on Mother's Milk from 1927 to 1930. For several years he was contributing editor of the section on diseases of children in *Progressive Medicine*. In the World War he served as a medical officer at Camp Sevier and later at Camp Jackson. He was a member of many medical societies and clubs.

Dr. McLean's compelling interest in medicine and first obligation were his patients. He believed strongly with his old master, Dr. Holt, who remained an active professional influence throughout his life, that

the most valuable medical experience comes from private practice. Through years of intensive effort he amassed a practical knowledge of children and their diseases and developed an excellence in the art of practice that few achieve. He was singularly dedicated to the prevention of unnecessary surgical procedures. Patients were ever fascinating problems, and he did not spare time, energy or expense in their behalf. Only the call of the outdoors could occasionally entice him from these duties, and in his later years he found great happiness on the farm, in the woods and in the cry of the wild duck over the rushes or the flash of the mountain trout in the stream.

From his earliest hospital days, Dr. McLean was interested in clinical investigation and made many substantial contributions in numerous publications. His wide medical interest as a practitioner and abundant clinical experience humanized his endeavors and urged him to the essentially practical. He was happier in clinical investigation with patients than in laboratory investigation of biologic phenomena. In his later years he turned in part to the laboratory in an investigation of the morphologic and roentgenologic changes of the growing skeleton in congenital syphilis. This painstaking and comprehensive study is authoritative in this field.

Stafford McLean was a strong man of plain and direct manner. His outstanding qualities were a tireless devotion to his professional obligations and a rugged loyalty to his friends. To those who knew him well, his loss is irreparable. No one will follow who will present the same combination of robust enthusiasm, steadfast determination, honest friendliness and human sympathy. His sudden passing stuns us with a sense of great personal loss and solid regret. His memory will long be cherished in the many spheres of his good works.

J. C.

Abstracts from Current Literature

Pathology, Bacteriology and Biochemistry

SOME OBSERVATIONS ON THE CIRCULATION IN EXPERIMENTAL MITRAL STENOSIS. JOHN H. POWERS, COBB PILCHER and MORRIS A. BOWIE, Am. J. Physiol. **97**:405 (June 1) 1931.

Observations were made on some phases of the circulation of five male dogs with experimental mitral stenosis. The cardiac output of four of these animals ranged between 104 and 230 cc. per kilogram per minute; the average was 171 cc. These figures are within the range of normal. The output of the fifth animal was distinctly elevated, being 323 cc. per kilogram per minute. The basal pulse rate was increased in four instances and normal in the fifth. The blood pressure was elevated in only one case. An increase in the percentage of red blood cells occurred at the expense of the plasma. The size of the heart, as determined by the roentgen shadow, showed a progressive enlargement in all five dogs. No significant changes were observed in the electrocardiographic tracings. Observations on the control animal showed no variations from the normal.

NOURSE, Cleveland.

CALCIFICATION FOLLOWING MASSIVE DOSES OF VIOSTEROL IN ACUTE EXPERIMENTAL BOVINE TUBERCULOSIS OF GUINEA PIGS. T. T. WALKER and T. D. SPIES, Am. Rev. Tuberc. **24**:65 (July) 1931.

Experimental guinea-pigs were inoculated (intravenously) with 1 cc. of a heavy saline suspension of a ten-day culture of highly virulent bacilli of bovine tuberculosis. After twelve days a preparation of viosterol having 10,000 times the antirachitic potency of cod liver oil was given by mouth: 18 minims (1.11 Gm.) on the twelfth day, 9 minims (0.55 Gm.) on the thirteenth day and 9 minims on the sixteenth day after inoculation. All of the animals died in from fifteen to twenty-two days after the injection of tubercle bacilli. Examination disclosed extensive calcification within the tubercles in the lungs, which were caseous in five of nine animals. There was no calcification in the control animals. This calcification was much more marked than that which occurs in similar lesions of tuberculosis without the use of viosterol. Calcium was also deposited in apparently normal tissue of the heart, liver and kidneys of the tuberculous animals treated with viosterol.

SMITH, Ogden, Utah.

THE RÔLE OF THE ANTERIOR LOBE OF THE PITUITARY GLAND IN GROWTH, WITH SPECIAL REFERENCE TO THE TEETH AND MAXILLAE. WILLIAM G. DOWNS, Arch. Path. **12**:37 (July) 1931.

In studying the effect of the pituitary gland in growth, three series of experiments were made. In the first, seventy-five mice of a closely inbred colony were divided into three groups, one of which was fed the anterior lobe of beef hypophysis daily, the second, liver in similar quantities, and the third, the usual diet for these animals. The first two groups gained at a slightly higher rate, but no more than might be due to the higher intake of protein. Attention was therefore turned to the injection of the extract of the anterior lobe of the pituitary prepared according to Evans' instructions. Analysis of the results showed that the mice receiving the extract gained at a considerably more rapid rate than their littermates and that they had a higher water and a higher ash content than the controls,

with a somewhat decreased fat content. The effect on dentition was to accelerate this process markedly. There was also some splenomegaly. A third series of studies was made on dogs, which also included a group on which hypophysectomy had been performed. In each case the injections caused greatly accelerated growth, splenomegaly and acceleration in dentition. In the hypophysectomized dogs, the changes were the opposite.

LESLIE, Evanston, Ill.

OBSTRUCTIVE PULMONARY ATELECTASIS. W. E. ADAMS and H. M. LIVINGSTONE, Arch. Surg. **23**:500 (Sept.) 1931.

To clear up a difference of opinion as to the etiologic factors in obstructive pulmonary atelectasis, the authors carried on experiments in dogs by artificial obstruction of the air passages. Complete and partial obstruction was brought about by cauterization, and the degree of atelectasis was noted at autopsy. Observations were also made to determine if the degree of respiratory effort had anything to do with the development of pulmonary atelectasis. From the numerous experiments the authors concluded: 1. Complete obstruction of the air passages of an entire pulmonary lobe is essential to the production of massive atelectasis. 2. Complete obstruction of the air passages of part of a lobe is not accompanied by atelectasis of the obstructed part. 3. No particular form of respiration is essential to the production of massive collapse. 4. Communications appear to be present between the alveoli of adjacent lobules of a pulmonary lobe in dogs. 5. Pulmonary suppuration is not associated with obstructive pulmonary atelectasis produced experimentally in dogs.

KAISER, Rochester, N. Y.

STUDY OF THE ACTION OF IRRADIATED ERGOSTEROL AND OF ITS RELATIONSHIP TO PARATHYROID FUNCTION. N. B. TAYLOR, C. B. WELD, H. D. BRANION and H. D. KAY, Canad. M. A. J. **25**:20 (July) 1931.

This paper gives the experimental evidence on which the authors base their opinion that there is a close relationship between overdosage effects of irradiated ergosterol and parathyroid function. They believe that there is a direct stimulation of the parathyroid by the sterol. The symptoms and postmortem observations on the blood following overdosage with irradiated ergosterol are indistinguishable from those resulting from lethal doses of parathyroid-Collip. The chemical composition of the blood, so far as this has been investigated, is affected in an almost identical manner by either substance.

MOORE, Omaha.

THE PHOSPHATASE OF FETAL BONE. EARL J. KING and G. EDWARD HALL, Canad. M. A. J. **25**:44 (July) 1931.

The experiments described by the authors were devised to verify previous experimental work done by Martland and Robinson and Kay and Robinson. In previous work it had been demonstrated that the ossifying parts of the bones contained a phosphatase enzyme which liberated phosphorus from its organic combination in the plasma and caused it to be deposited as calcium phosphate. The results obtained in this work verified the previous results; namely, large amounts of phosphatase were found in parts where active ossification was in progress and smaller amounts in the regions where the process was just beginning, while little, if any, enzyme activity was apparent in the epiphyseal and other parts where ossification had not yet begun.

MOORE, Omaha.

SOME DIFFICULTIES IN IMMUNIZATION WITH VACCINES. E. G. D. MURRAY, Canad. M. A. J. **25**:125 (Aug.) 1931.

The author deals in a general way with the problems of immunity. The first important point to realize in considering active immunity is that the immunity

response is the product of an interaction between the recipient animal and the antigen, and that, in a general way, neither one is more important than the other. Some persons will respond to certain antigens and not to others, and some respond poorly or hardly at all to immunization. Patients may not recover from infection when it can be demonstrated that they have developed a marked antibacterial immunity to the organisms invading them. The existence of an inherited resistance to infection which is not specific in nature is suggested in some cases. There is ample evidence to believe that malnutrition lowers resistance to spontaneous and induced infection, but "there is little evidence that nutritional defects disturb the antibody forming mechanisms." These unanswered questions lie within the province of clinical medicine.

The author also stresses the importance of proper selection of strains of organisms, the necessity for a medium prepared according to the bacteria grown and the confusion in dosage. Vaccines will have their important place in therapeutic procedures, but probably not until some of the questions brought out have been solved.

MOORE, Omaha.

THE CHEMISTRY OF DIPHTHERIA TOXIN PRODUCED IN SYNTHETIC MEDIUMS. MARY E. MAVER, J. Infect. Dis. **49**:1 (July) 1931.

The conclusion is reached in this article that the toxic fraction in diphtheria toxin is closely associated with a protein, although the conclusive proof of the protein nature of this toxin must await the production of a crystalline protein toxin. Certain chemical tests indicate that a protein is synthesized simultaneously with the production of diphtheria toxin in synthetic mediums.

TOOMEY, Cleveland.

THE ATTENUATION OF THE DIPHTHERIA BACILLUS IN SYNTHETIC MEDIUMS: OBSERVATIONS ON DISSOCIATION, ANTIGENIC RELATIONS AND FERMENTATIVE REACTIONS. MARY E. MAVER, J. Infect. Dis. **49**:9 (July) 1931.

This is a long descriptive article on the morphologic dissociative changes occurring in the diphtheria bacillus planted in various mediums. Of the thirty-one freshly isolated strains, twenty-five were dissociated into cocci after the first or second transfer to synthetic mediums. The appearance of attenuated colonies, the relationship between different strains and the behavior of various cultures under different conditions are described. This is a very illuminating article to those who feel that a diphtheria bacillus must conform to a certain morphologic Westbrook standard.

TOOMEY, Cleveland.

THE FECAL FLORA OF ADULTS WITH PARTICULAR ATTENTION TO INDIVIDUAL DIFFERENCES AND THEIR RELATIONSHIP TO THE EFFECTS OF VARIOUS DIETS: II. INDIVIDUAL DIFFERENCES IN RESPONSE TO SPECIAL DIETS. AGNES GOLDMAN SANBORN, J. Infect. Dis. **49**:37 (July) 1931.

This report is based on the results obtained in fifteen psychopathic patients given various diets. The article is more or less descriptive. One conclusion is stressed: that any transformation of the fecal flora is dependent in part on the character and stability of the native flora. A high carbohydrate or protein diet tends to simplify the aerobic flora in the acidophil and colonic direction, respectively. Transformation of the fecal flora in the acidophil direction generally occurs independent of age. Strains of Bacillus acidophilus almost completely suppress native strains although the latter may be numerous, but when this therapy is stopped the foreign strain dies quickly and the native strains are revivified. The author wisely does not draw any categorical conclusions.

TOOMEY, Cleveland.

THE DESTRUCTION OF MICRO-ORGANISMS IN THE GASTRO-INTESTINAL TRACT. B. E. MONTGOMERY, A. K. BOOR, LLOYD ARNOLD and OLAF BERGEIM, J. Infect. Dis. **49**:104 (Aug.) 1931.

The authors gave yeast to normal persons and studied the viability of the yeast cells in stools of normal persons under various conditions. The first experiments, performed in vitro, showed that the killing action of artificial gastric juice (hydrochloric acid, from 0.1 to 0.36 per cent) is variable, from 23 to 99 per cent of the yeast cells being killed. Pepsin occupies a minor rôle in this cell destruction. Unboiled human gastric secretion brought about nearly complete destruction of the yeast cells in four hours. On an empty stomach, 75 per cent of the yeast cells passed through the stomach alive; when given with water, a greater proportion passed through. Under varying conditions from 50 to 95 per cent of the ingested yeast cells pass through the stomach alive, the greater number when given with fluids like water and the lesser when given with meat. Normal human pancreatic juice killed about 50 per cent of the yeast cells in sixteen hours. When injected into intestinal segments of dogs, a destruction of from 20 to 40 per cent of the cells was shown. Compressed bakers' yeast when fed to man is excreted alive in variable amounts from none to 19.5 per cent, the majority of cases giving a 1 per cent rating. In dogs given yeast daily, about 30 per cent was excreted in a living state. There is a diffusible, partly thermostable destructive agency in the normal stool, since yeast cells incubated with fresh human feces were in most instances almost all killed in twenty-four hours.

TOOMEY, Cleveland.

PARATHYROIDECTOMY AND VITAMIN D. A. ARTHUS and A. JEDRZEJOWSKA, Compt. rend. Soc. de biol. **107**:105 (May 18) 1931.

Several series of rabbits were fed viosterol, from 8 to 16 drops, for eight days prior to thyroidectomy. The animals survived the operation without tetany and with maintenance of a blood calcium content of 5.6 mg. or more. Animals not given viosterol died within twenty-four hours from tetany, at the same time showing a low blood calcium content. The experiment was checked in various ways to prove that vitamin D protected rabbits from tetany after parathyroidectomy.

WAHL, Cleveland.

CALCIFYING ACTION OF IRRADIATED ERGOSTEROL (VITAMIN D) IN THE LESIONS PROVOKED BY THE INJECTION OF B C G INTO THE TESTICLE OF THE RABBIT. C. LEVADITI and LI YUAN PO, Compt. rend. Soc. de biol. **107**:122 (May 18) 1931.

Eight rabbits received intratesticularly 5 mg. of B C G. Four animals were used as controls; the other four received by mouth 2 mg. of ergosterol per kilogram of body weight. After about eight days the animals were killed and the testes were examined pathologically. Definite calcification occurred in the epithelioid and giant cells, and in some instances concretions were found containing the bacilli. Calcification likewise was found in the seminiferous tubules. Further experiments, conducted in a similar manner, but with virulent tubercle bacilli, showed an even greater calcification process in the testes. The intensity of the calcification appears to be in proportion to the virulence of the tubercle bacilli infecting the testes. Apparently, this is a very rapid method for the production of calcification in living tissue.

WAHL, Cleveland.

THE EFFECT OF SERUM INJECTIONS ON THE EOSINOPHIL CURVE. ALEXANDRINE STROBL, Monatschr. f. Kinderh. **50**:325, 1931.

In tests on fifty children the author confirmed her previous observation that the injection of 0.5 cc. of serum is followed in normal children by an increase of

eosinophils within forty-eight hours, with a rapid return to normal. In children with an exudative diathesis the eosinophils remain stationary or drop and do not return to normal until from the fourth to the seventh day.

GERSTLEY, Chicago.

SIMULTANEOUS DETERMINATIONS OF CALCIUM AND PHOSPHORUS IN THE BLOOD SERUM OF BABIES WITHOUT SINUS PUNCTURE. E. FREUDENBERG, Ztschr. f. Kinderh. **51**:267, 1931.

Warkany's modification of the Bell-Doisy-Briggs method of determining calcium and phosphorus in 0.2 cm. of blood serum has justified itself. A slight improvement is added by Freudenberg, by which the calcium can be measured with a maximum error of ± 10 per cent; in three fourths of the cases, ± 5 per cent. To determine the calcium and phosphorus simultaneously, 0.8 cm. of serum is necessary; for double analysis, 2 cm. This quantity of blood can be taken from the heel, anesthetized with ethyl chloride, by a small incision if the veins of the scalp are not available.

EMERSON, Boston.

Nutrition

THE ULTRA VIOLET ABSORPTION SPECTRUMS OF HEMOLYZED BLOOD CORPUSCLES IN RELATION TO RICKETS. R. C. GIBBS, J. R. JOHNSON and C. V. SHAPIRO, Am. J. Physiol. **97**:243 (May 1) 1931.

The authors investigated the absorption spectra of hemolyzed solutions of the red blood corpuscles of healthy and rachitic rats to determine whether the differences reported by Suhrmann and his collaborators could be used as a quantitative estimation of the extent of the development of rickets in animals. Their results showed that the absorption spectra of the two groups are entirely identical, and that the change of absorption reported by Suhrmann and his collaborators was probably caused by some factor not necessarily associated with rickets. They further advance experimental and theoretical evidence to show that the change of absorption under these conditions reported by the investigators can be attributed to a scattering of light by suspended matter in the solutions and that no chemical change of the hemoglobin is involved.

NOURSE, Cleveland.

VITAMIN A POTENCY OF RETINAL TISSUE. ARTHUR M. YUDKIN, MAX KRISS and ARTHUR H. SMITH, Am. J. Physiol. **97**:611 (July 1) 1931.

The retina has been shown to be a rich source of vitamin A. From 20 to 30 mg. of dried normal tissue per day will alleviate the characteristic symptoms of a deficiency of vitamin A in young rats. When given from the beginning with a ration deficient in vitamin A, 20 mg. of dried retina will promote normal growth and physiologic well-being in young rats. Recent studies suggest that the vitamin A (or its precursor) localized in the retina bears a more or less structural relationship to the retinal pigment. The choroid contains little, if any, vitamin A.

NOURSE, Cleveland.

THE EFFECT OF DIFFERENT PER CENTS OF PROTEIN IN THE DIET: VI. WEIGHT OF MOTHERS DURING GESTATION AND LACTATION. JAMES ROLLIN SLONAKER, Am. J. Physiol. **97**:626 (July 1) 1931.

The author fed five groups of rats carefully prepared synthetic diets containing 10, 14, 18, 22 and 26 per cent protein, respectively. He presents the results of these diets as reflected in the gestation and lactation weights of those mothers the weights of which were taken daily during these periods. The weight gained during gestation was greatest with the low protein diets, and became less as the percentage of protein was increased. During the nursing period, the loss of weight was greatest in the group on the diet containing the least protein, and became less as

the percentage of protein in the diet increased. Data indicate that the quantity and quality of milk secretion were poorest in the group receiving 10 per cent protein, and that they increased as the protein content of the diet increased.

NOURSE, Cleveland.

COD LIVER OIL EMULSIFIED IN AN EXTRACT OF GERMINATING GRAINS: ITS TOLERANCE BY THE INFANT GASTRO-INTESTINAL TRACT AND ITS PROPHYLACTIC VALUE. B. WINSTON JARVIS, Arch. Pediat. **48**:502 (Aug.) 1931.

The author finds that an emulsion of cod liver oil in a concentrated extract of the germinating grains of wheat, oats and malted barley is a mixture exceptionally well tolerated by the infant's gastro-intestinal tract. This emulsion contains vitamins A, B and D and lacks vitamin C, which should be included by means of adequate amounts of orange or tomato juice. When the mixture was started at from 6 to 8 weeks of life and administered as a routine measure, deficiency diseases were apparently prevented in the 150 cases studied. In no instance was a gastro-intestinal upset attributable to the medication.

WADDELL, University, Va.

COLIC IN INFANCY, IN THE SECOND TRIMESTER: REPORT OF A CASE. A. J. SCOTT, California & West. Med. **35**:107 (Aug.) 1931.

Colic in infants from 3 to 6 months old is rare, as compared with that in infants up to 3 months, in whom it is fairly common. When it occurs in the second trimester, a careful inquiry should be made to determine its etiology. A careful history and a complete physical examination with the infant stripped are essential. Etiologic factors to be considered should include: indigestion due to either a high fat or a high sugar content in the diet or to food not suitable for the particular infant; cerebral birth injuries, in which spastic signs and muscle rigidity may be associated with an inability to care for the food properly; pyuria and renal colic; inflammation of the ear and mastoids; intussusception, and strangulated hernia. Angioneurotic edema is a rare cause. Congenital anomalies as a cause of colic are rather rare, but strictures, adhesions, mesenteric cysts and Meckel's diverticulum may be the cause. A case is reported in which the last-named condition caused abdominal pain, fussiness and vomiting in an infant of 4½ months, the anomaly being found at operation.

DICKEY, San Francisco.

RECENT ADVANCES IN CALCIUM METABOLISM. A. CANTAROW, Internat. Clin. **1**: 34 (March) 1931.

The functional activity of either the parathyroid hormone or the antirachitic factor is conditioned by the presence of the other factor, in adequate amount, and, in addition, on an adequate supply of calcium and phosphorus in the diet. Hyperparathyroidism has been observed most strikingly in association with the diffuse form of osteitis fibrosa cystica. The diagnosis of hyperparathyroidism depends on the following findings: (1) hypercalcemia; (2) hypophosphatemia and (3) an increased urinary excretion of calcium and (4) of phosphorus. The symptomatic and objective manifestations include muscular hypotonia, decreased electrical excitability, polyuria, anorexia, constipation, metastatic calcification in various situations and nephrolithiasis. The clinical entity is amenable to treatment by parathyroidectomy.

MILLER, South Bend, Ind.

THE INFLUENCE OF AN EXCLUSIVE MEAT DIET ON THE FLORA OF THE HUMAN COLON. JOHN C. TORREY and ELIZABETH MONTU, J. Infect. Dis. **49**:141 (Aug.) 1931.

Three men were given an exclusive meat diet—two for thirteen months and one for ten days—and the colonic flora studied. The fat in the diet averaged from one and a half to one and three-fourths times the protein by weight, and

all available carbohydrate was in the meat, from 5 to 10 Gm. a day. The specimens obtained while the subjects were on this diet were mildly acid, aromatic and inoffensive, and usually had a p_H of from 7.0 to 6.0. A decrease in bacterial content took place, from 15 per cent in one to 50 per cent in another. The depressed bacteria were those largely dependent on carbohydrates for their metabolism (Bacillus acidophilus, Bacillus bifidus, enterococci, streptococci, etc.). Bacillus coli was reduced in number, while the percentage of hemolytic B. coli was increased the first few weeks, the virulence remaining the same. Bacillus welchii was increased for several months. Proteolytic anaerobes were not present in the stools. Proteus was absent in one and practically absent in the other while Micrococcus zymogenes was increased. There was no definite consistent increase in the proteolytic action of the whole flora on a cooked meat medium. The authors feel that their observations tend to show that an exclusive meat diet, even continued for a long period, is not necessarily conducive to the establishment of an obligate proteolytic flora in the human colon.

TOOMEY, Cleveland.

EFFECT OF VITAMINS A AND D ON RESISTANCE TO INFECTION. LYMAN C. BOYNTON and W. L. BRADFORD, J. Nutrition **4**:323 (Sept.) 1931.

Ninety-one healthy 4 weeks old white rats were used in the experimental series. Forty-six were put on the vitamin A-free diet and forty-five were fed the rachitic ration. Twenty-three rats of the vitamin A group were used as controls and given cod liver oil. The twenty-two controls in the vitamin D group were given viosterol. A twenty-four hour broth culture of Bacillus mucosus-capsulatus was injected intraperitoneally in all the animals, the infecting dose having been previously determined in a series of stock animals. Injections were made at four, six, eight and ten week intervals in the vitamin A group and at four, six and eight week intervals in the vitamin D group. The results definitely indicated that animals on a vitamin A-deficient diet have a markedly decreased resistance to infection, and that this decreased resistance to infection appears some time before the ordinary physical signs of vitamin A deficiency are apparent, and may be an early warning that a vitamin A depletion exists. Rats on the vitamin D-deficient diet showed no great difference in susceptibility as compared to controls protected by viosterol.

MUNNS, Winnetka, Ill.

STUDIES IN PROTEIN NUTRITION OF THE CHICK: I. THE INFLUENCE OF DIFFERENT PROTEIN CONCENTRATES ON THE GROWTH OF BABY CHICKS WHEN FED AS THE SOURCE OF PROTEIN IN VARIOUS SIMPLIFIED DIETS. W. D. MCFARLANE, W. R. GRAHAM, JR., and G. E. HALL, J. Nutrition **4**:331 (Sept. 1) 1931.

An attempt was first made to procure a synthetic basal diet that would satisfy the vitamin requirements of the chick and yet contain the minimum amount of protein. This diet was supplemented with equal amounts of crude protein from different protein supplements: buttermilk powder, fish meal, cod liver meal, meat meal and tankage. Proper growth was not attained among any of the groups of chicks until substances containing vegetable protein were added to the diet. Only a very small amount of the vegetable protein seemed necessary to cause a marked improvement in the growth of the chicks. This beneficial effect may be due either to the vegetable protein or to some as yet unidentified substance or substances associated with vegetable material.

MUNNS, Winnetka, Ill.

FACTORS WHICH DETERMINE RENAL WEIGHT: XII. THE NITROGEN INTAKE AS VARIED BY THE ADDITION OF UREA TO THE DIET. L. L. MACKAY, E. MACKAY and T. ADDIS, J. Nutrition **4**:379 (Sept.) 1931.

The author showed in earlier work that when the food protein was casein, the weight of the kidneys in rats could be predicted from measurements of the casein

consumption. The nitrogen of casein is excreted almost entirely as urea. Therefore, if this is the only mechanism underlying the casein-kidney weight relationship, the same curve should be produced when urea is substituted for equivalent amounts of casein in the food.

In two groups of experiments on male rats of exact and known age, it was found that the addition of urea to the diet increased the weight of the kidneys. However, the increase in renal weight was less than that produced by the administration of protein instead of urea.

MUNNS, Winnetka, Ill.

FOOD INTAKE IN PREGNANCY, LACTATION AND REPRODUCTIVE REST IN THE HUMAN MOTHER. C. F. SHUKERS, I. G. MACY, E. DONELSON, B. NIMS and H. A. HUNSCHER, J. Nutrition **4**:399 (Sept.) 1931.

In this interesting study, one of a series of several similar studies, the authors were able to observe the dietary requirements of three women during the complete reproductive cycle. The three subjects were known to be physiologically well adapted to the requirements of pregnancy and lactation. The women were allowed to select their own diets, and careful records were kept of the amounts of fats, carbohydrates, proteins, calcium and phosphorus ingested together with the caloric values. Three periods, pregnancy, lactation and postlactation, were observed.

The findings indicate that the food requirements for pregnancy and for recuperation during the postlactation period are of approximately the same magnitude. Food consumption was reduced near the close of pregnancy. Lactation increased the food demands approximately 60 per cent over those of pregnancy. During lactation the daily food intake varied decidedly. The maximum was at times twice as large as the minimum. These findings tend to agree with similar observations made on rats.

MUNNS, Winnetka, Ill.

GLYCOGEN AND FAT FORMATION IN RATS: V. CARBOHYDRATE-FREE DIETS. ESTHER M. GREISHEIMER, J. Nutrition **4**:411 (Sept.) 1931.

Fifty young rats were kept on MacCallum's stock diet 1 for a period of one week, and then were divided into groups of ten and fed the test diets of lard, lactose-free casein and salt mixture 185 for three weeks. The diets were (1) 87.5 per cent (of total caloric value) lard and 12.5 per cent casein, (2) 75 per cent lard and 25 per cent casein, (3) 50 per cent lard and 50 per cent casein, (4) 25 per cent lard and 75 per cent casein and (5) 12.5 per cent lard and 87.5 per cent casein. The water intake was decreased over one third on diet 1, but was increased from one seventh to one third on diets 2, 3, 4 and 5, respectively. The caloric intake was increased on diets 1 and 2 and decreased on diets 3, 4 and 5. Rats on diets 1, 2 and 3 gained steadily in weight. Those on diets 4 and 5 lost weight during the first week, but gained slowly during the second and third weeks. The liver in relation to body weight was significantly heavier in rats on diets 4 and 5, and the percentage of liver glycogen increased as the casein content of the diet increased. The liver lipid content decreased as the percentage of lard in the diet was decreased.

MUNNS, Winnetka, Ill.

PHENOMENA OF RETARDED GROWTH: EDITORIAL REVIEW. ARTHUR H. SMITH, J. Nutrition **4**:427 (Sept.) 1931.

Heredity is a primary factor governing growth, as the final size of the organism is limited by the particular germ plasm of the species. However, environment is an important factor in growth, and the nature and amount of food materials supplying the growing organism may markedly change the phenomenon of growth. Interference with normal growth in young animals may follow limitation in quantity of food, limitation of ingested water, restriction of protein consumed or limitation of certain necessary amino-acids or inorganic salts in the diet. This

knowledge is available from the results of numerous feeding experiments conducted by competent investigators. To sum up, it appears that the restriction of any constituent known to be indispensable in the diet is followed by interference with growth in the young and by difficulty of maintenance in adult animals. Other experimental work reveals that growth may also be influenced by the efficiency of removal of waste products of metabolism.

An interesting phenomenon of retarded growth is the retention, on the part of the experimental animal, of the ability to resume an increase in body weight when nutritive conditions once more become favorable. Although an increase in body weight may be greatly retarded by adjustment of the rations, the growth of the bones persists; furthermore there occurs a concomitant increase in fresh weight of the bones, often in normal proportions or degree. This phenomenon apparently occurs at the expense of other tissue constituents. A marked change in the composition of the bones may occur, the bones of the restricted animal containing a much higher percentage of water and practically no fat. There is only slight reduction in protein content, and the percentage of ash remains the same. In dogs maintained at a markedly subnormal weight by underfeeding, the internal organs, with the exception of the brain, retained their normal weights and normal relation to body weight. The brain continued to grow until it doubled its normal relative weight. However, it is possible to produce by various forms of dietary restriction a disproportion in size of various body organs. There are few changes in the composition of the blood during inanition. Marked changes may appear if there is a definite cessation of growth.

Many experiments have been performed to determine the effect of dietary restriction and stunting on behavior. In general, it may be said that in measures of behavior involving speed, the restricted animals tend to resemble normal animals of the same body weight. While they are in the problem box they approach more closely the age controls.

MUNNS, Winnetka, Ill.

VITAMIN G IN ROOT AND LEAF VEGETABLES. PAUL L. DAY, South. M. J. **24**:876 (Oct.) 1931.

Fresh beets, carrots, potatoes and turnips have been found to contain small but measurable quantities of vitamin G, being approximately equivalent as a source of the vitamin. Beet, carrot and turnip tops have been found to be good sources of vitamin G, containing from four to six times as much vitamin as the corresponding roots. Winter spinach appeared to be a somewhat poorer source of the vitamin than the other leaves examined, which were grown in the summer months.

SCHLUTZ, Chicago.

HYPERVITAMINOSIS-D, WITH REPORT OF A FATAL CASE IN A CHILD. LEWIS THATCHER, Edinburgh M. J. **38**:457 (Aug.) 1931.

Thatcher briefly reviews the opinions concerning the calcifying factors that are now recognized. The literature is mentioned, dealing with the toxic effects that have been reported from excessive doses of cod liver oil, ultraviolet irradiation and irradiated ergosterol. The author then reports the history of an 18 months old child at the Royal Hospital for Sick Children, who died after five months' treatment with therapeutic ergosterol. The course and the autopsy furnished interesting suggestions as to danger from excessive treatment. The conditions of the child just before death were those of pallor, body frailty, slightness of the bones, softness of the muscles and an open fontanel, but no sign of rickets or its sequelae. The diagnosis was complicated by renal lesions, so that pyelonephritis and a possible underlying congenital renal abnormality had to be considered. There were pus and red blood cells in the urine, along with granular casts, albumin and acid bodies. The blood urea content reached 90 mg., and the breathing was of the hyperpnea type. The child lived only ten days after reaching the hospital.

Miss Macgregor, pathologist, reported the autopsy findings as similar to those in experimental hypervitaminosis D, as well as to those in Putschar's case. The changes were not so far advanced, however, and were limited to calcium deposits in the kidneys, found at first in the collecting tubules where the calcium concentration in the secretion is the highest. There was proliferation of fibrous tissue around some of the deposits. The pyogenic infection was probably a complication. No rickets had ever been present. The liver was involved in an extensive fatty degeneration.

The author feels that no other explanation of the findings can be given than that of hypervitaminosis D. Four teaspoonfuls of viosterol emulsion were given daily during the summer months at the seaside to a child who was kept out of doors. This is an extended period for such vigorous treatment, especially at the time of the year. Children free from rickets are more susceptible to the drug. Calcium salts were possibly mobilized from the bones as an effect of the excessive medication. Demineralization on a deficient diet and an excess of blood inorganic phosphate, which is even higher in the summer, are known clinically and experimentally. Intensive treatment for the cure of rickets should not be protracted. Symptoms of a lack of tolerance for ergosterol are anorexia, diarrhea, fever, a drowsy mental state, progressive loss of weight, cachexia, pallor, albuminuria, and pyuria, hypercalcemia and, later, hyperphosphatemia. The bones may show roentgenologically an excessive calcification. Infants may have an idiosyncrasy for irradiated ergosterol which becomes a definite danger, as the drug is toxic in large doses over a long period of time. Nonrachitic infants are more susceptible, and feeble babies should not receive the drug, especially in the summer months.

NEFF, Kansas City, Mo.

A CONSIDERATION OF THE CATARRHAL STATES IN RELATION TO DIET. J. H. P. PATON, Edinburgh M. J. **38**:468 (Aug.) 1931.

Dr. Paton, St. Leonard's School for Girls, St. Andrews, has investigated the incidence of catarrhal illness in that school for the last twenty-five years. He discusses the effect of food deficiency, occurring often as lowered resistance to infection, especially tuberculosis, or to avitaminosis. During the World War the diet for Scotland was much restricted. Excess diet may increase the tendency to certain infections. Maitland Ramsey, in 1909, advised the removal of all sugar from the diet in phlyctenular conjunctivitis. He reported the case of an 8 year old boy who had influenza in 1919 and who ever since had been subject to photophobia, follicular tonsillitis, cervical gland hyperplasia and nasal and bronchial catarrh. The eyegrounds showed congestion of the optic disks. The removal of sugar from the diet cleared up the catarrhal conditions. Cases of influenza were free from catarrhal complications during the periods when the use of sugar was restricted, such as in 1918. This was verified also in the author's study at the girls' school. He believes that the excessive consumption of sugar favors the catarrhal diathesis, and advises that in Scotland a stringent inquiry be made into the tolerance limits of this food stuff.

NEFF, Kansas City, Mo.

THE ANTIRACHITIC VALUE OF IRRADIATED YEAST. S. K. KON, Lancet **2**:579 (Sept. 12) 1931.

The paper deals with the evaluation of the antirachitic potency of irradiated yeast by means of the rat test. The results indicate that irradiated yeast retains its antirachitic properties for a long time (at least ten months), and that it can be kept at ordinary temperature and exposure to air. A toxic effect could be elicited in rats by the prolonged administration of a modified Steenbock stock diet containing 10 per cent by weight of irradiated yeast.

LANGMANN, New York.

SEASONAL INCIDENCE OF CRANIOTABES. A. B. MARFAN, Nourrisson **19**:176 (May) 1931.

In recent years numerous authors have claimed that craniotabes is due to rickets and that it can definitely be traced to inadequate exposure of young infants to sunlight. In order to prove or disprove this hypothesis, Marfan studied 3,354 infants with reference to the incidence of craniotabes during the summer and winter months. While the number of babies with craniotabes was slightly higher during the winter months in one hospital, the opposite was true of another hospital. In any event the percentage variation was so slight that it did not support the contention that craniotabes can be blamed on a lack of sunshine.

McCLELLAND, Cleveland.

ANEMIA IN RICKETS. A. B. MARFAN, Nourrisson **19**:209 (July) 1931.

That rickets is accompanied by an anemia, all observers agree. Concerning the cause of this anemia there is a divergence of opinion. Many think that the anemia is nutritional, and that its occurrence in the infant with rickets is purely accidental. Marfan does not subscribe to this view. Neither does he believe that the anemia is secondary to the pathologic condition present in the rachitic bones. He holds that the same factors that cause rickets, namely, prolonged infections or intoxications are also responsible for the anemia.

The anemia associated with rickets may be slight or severe, but is almost always of the secondary type, the lowering of the hemoglobin being more marked than the fall in the red blood cells, giving a lower color index. The leukocytes are increased moderately (from 13,000 to 16,000), especially the lymphocytes and mononuclears. If the anemia becomes more marked, it may even present the picture of the pseudoleukemic anemia of von Jaksch.

To cure the anemia of rickets, antirachitic remedies do not suffice. The underlying causes of both the rickets and the anemia must be corrected. For Marfan these are congenital syphilis, tuberculosis, especially scrofula, chronic bronchopneumonia, chronic nasal diphtheria, pyodermias or the absorption of toxins produced by prolonged digestive disturbances.

McCLELLAND, Cleveland.

INFLUENCE OF ULTRAVIOLET RAYS ON THE ELIMINATION OF URIC ACID. A. CABITTO, Riv. di clin. pediat. **29**:106 (Feb.) 1931.

The author studied the elimination of uric acid in three children, 5, 8 and 9 years of age, before and after ultraviolet irradiation. The uric acid in the urine diminished in amount on the day of the treatment; it then rose to considerably more than normal for several days, gradually falling to normal. A similar observation was made on a puppy. In these tests, a purin-free diet was given. To one child on a purin-rich diet, no change in the uric acid elimination was observed. The author ascribes his results to an excitation of the metabolic activities of the cell nuclei.

HIGGINS, Boston.

VARIATIONS IN THE BLOOD SUGAR CURVE FROM FEEDING IRRADIATED CARBOHYDRATES. P. GORINI, Riv. di clin. pediat. **29**:138 (Feb.) 1931.

Observations were made with irradiated and nonirradiated solutions (from 10 to 15 per cent) of three monosaccharides (dextrose, galactose and levulose), of two disaccharides (lactose and maltose) and of one polysaccharide (starch). The blood sugar curves of from two to four children, from 2 to 5 years old, were determined following the ingestion of each carbohydrate. The curves of the same children were then determined with the irradiated solution of the same carbohydrate. One gram of carbohydrate per kilogram of body weight was given. The feeding of an irradiated solution of disaccharides and polysaccharides renders the blood

sugar curve similar to that found normally with the feeding of a monosaccharide; the peak of the curve is higher and occurs sooner. The feeding of an irradiated solution of a monosaccharide was followed by a flatter blood sugar curve, which rose sooner than in the nonirradiated controls.

HIGGINS, Boston.

THE PATHOGENESIS OF MALARIAL RICKETS. D. CORDA, Riv. di clin. pediat. **29**:666 (Aug.) 1931.

In endeavoring to find the cause of malarial rickets the author determined the calcium and phosphorus content of the blood of twenty-six children with malaria; only six showed rachitic deformities, the other twenty having acute malaria. The results showed hypercalcemia (mean, 13.0 mg. of calcium per hundred cubic centimeters) and hypophosphatemia (mean, 3.5 mg. of phosphorus per hundred cubic centimeters). Corda concludes that malarial rickets is caused by two factors: (1) a cellular lesion of the cartilage from the malarial toxin, and (2) a metabolic disturbance from the high calcium: phosphorus ratio in the blood, which may be the result of a disturbance of the endocrine organs by the malarial parasites.

HIGGINS, Boston.

THE IMPORTANCE OF THE DIFFERENT PROTEINS IN INFANT FEEDING: A NEW FEEDING FOR INFANTS. C. COCCHI, Scritti med. dedicati a Carlo Comba, ediz., Riv. di clin. pediat., 1929, p. 613.

To supply 1 Gm. of cystine, 380 Gm. of casein or 23 Gm. of lactalbumin are necessary. Therefore, in modifying cows' milk for infant feeding, care must be taken to furnish sufficient lactalbumin, if one is to obtain a sufficient diet. A diet with casein as 80 per cent of the total protein results in about 50 per cent greater excretion of nitrogen in the stools than when 50 per cent of the protein is given as casein and 50 per cent as lactalbumin, equal amounts of the nitrogen being fed. The author presents the following method of preparing a modification of cow's milk with high lactalbumin content (he speaks of it as "humanized milk"): "Take 1 liter of whole cows' milk; divide it into two equal parts; remove all the cream possible from one part, by skimming; add the cream to the other part. Add ferment (rennin) to the skimmed milk. Filter the curd through sterile gauze. Boil the whey to destroy the remaining ferment; then add it to the 0.5 liter of milk containing the added cream. Add 15 Gm. of sugar (cane) and 8 Gm. of powdered lactalbumin." The mixture then contains:

	Per Cent	Calories	Per Cent of Total
Casein	15	63	10.8
Lactalbumin	12	50	8.0
Fat	30	270	43.2
Sucrose	45	180	....
Lactose	15	60	38.0
Salt	5	..	....

The results of feeding the usual cows' milk formula (milk, rice water and sugar) and "humanized" milk were noted. The babies gained better on the "humanized" milk and retained more nitrogen.

HIGGINS, Boston.

STUDIES ON THE NORMAL AND UNDERDEVELOPED CHILD DURING THE FIRST TWO YEARS OF LIFE IN RELATION TO THE BODY SURFACE AS MEASURED DIRECTLY: I. ESTIMATED FOOD RATION. G. CAREDDU, Scritti med. dedicati a Carlo Comba, ediz., Riv. di clin. pediat., 1929, p. 669.

This article is a consideration of the value of different units of development in expressing food requirements. The integrator of Bordier is used for measuring directly the body surface; results using this method are sometimes as much as 20 per cent greater than when the DuBois calculation is resorted to. The minimum ration for growth of normal infants was found to be between 15 and 21 calories per square decimeter or between 95 and 118 calories per kilogram. For under-

developed infants, the ration was between 21 and 27 calories per square decimeter or between 116 and 183 calories per kilogram. The surface area gives an excellent index of the nutritional needs independent of age; this does not hold so true when weight is the index. In underdeveloped children, the body surface is also a closer index. The use of height as an index, as suggested by Variot, gives too high calculated rations for the young baby and too low for the baby over 4 months old. Pirquet's method using the sitting height yields too high rations for the normal baby and too low for the underdeveloped baby.

HIGGINS, Boston.

UNUSUAL OBESITY IN AN INFANT. J. M. MACERA, E. CUILLE and M. DE LA FUENTE, Arch. argent. de pediat. **2**:64 (Feb.) 1931.

The authors report a case of unusual obesity in an infant whose weight at birth was normal. The adiposity began to appear after the first month of life, so that at the age of 7 months the child's weight was 17 Kg., and at 16 months, 24 Kg. The only features of importance that could be obtained from the history were that the child was on an abundant high caloric diet and that a grandmother weighed 100 Kg. The authors further discuss the various theories of obesity in infants, and show photographs of the patient under discussion.

SCHLUTZ, Chicago.

COMMON INFANTILE ACETONEMIA. BUXÓ IZAGUIRRE, But. Soc. Catalana de pediat. **1**:64 (April) 1928.

Two cases of acetonemia in a brother and sister are presented, one having a severe meningismus. Their mother had "a hepatic insufficiency." The author considers the possibility of an inherited fat catabolism disturbance.

WATSON, Elmhurst, Ill.

HOSPITAL DYSTROPHY. J. C. NAVARRO, Rev. de especialid. **6**:23 (June) 1931.

The author discusses the possibilities involved in the failure of some infants to gain in hospitals, and presents an example of this type of child. He finally obtained results with injections of dextrose and the feeding of human milk.

SANFORD, Chicago.

B AVITAMINOSIS AND BERIBERI. J. SHIMAZONO, Ergebn. d. inn. Med. u. Kinderh. **39**:1, 1931.

The author reviewed the mode of onset of experimental beriberi in pigeons, rats and larger animals fed exclusively on polished rice or a diet deficient in vitamin B. He concluded that there seems to be some relation between the quantity of ingested carbohydrates and vitamin B. When birds ingest much carbohydrate, B avitaminosis appears more rapidly; for this reason birds do not develop beriberi as early when they are fed a high protein but low carbohydrate diet or when, on account of poor appetite, they eat very little.

Shimazono's results on the experimental production of beriberi in man are similar to those obtained in lower animals. Sooner or later, after several weeks but sometimes not after three months, evidence of B avitaminosis appears, the degree depending on the amount of the insufficiency. When the experimental subjects have a good appetite and consume much rice daily, some symptoms make their appearance earlier. The subjects become nervous, develop insomnia, become pale and do not appear happy. The appetite becomes poor and they consume less food. The anorexia may disappear, only to reappear soon in a more severe form. At first the subjects only lose appetite for rice, but later they also refuse other

vegetable and animal foods. Occasionally nausea and vomiting set in. They become constipated. Edema practically always appears; this is first visible on the shin and the dorsum of the foot. It may spread over the whole body. The face is puffed. The urine is free from sugar or albumin, and acetone bodies are seen only when the anorexia leads to actual starvation. In severe cases, a trace of albumin may appear in the urine. There is no loss in body weight on account of the developing edema. The cardiac action becomes labile; the pulse rate may become definitely or slightly accelerated. The heart may become enlarged to the right or left, or in both directions. The apex beat may become stronger and more diffuse. Definite cardiac hypertrophy and dilatation do not, as a rule, occur. The heart sounds, especially the systolic, often become dull and faint. Systolic blood pressure is, as a rule, unchanged in contrast to the diastolic, which is practically always lowered. Sooner or later signs of polyneuritis appear. At first there are tactile disturbances of the ankles and feet; then these may attack the wrists, circumoral region and hips; in other words, the involvement is the same as in real beriberi. Just as in true beriberi, the motor disturbances are not quite so well defined, although occasionally in experimental B avitaminosis one may see definite palsy of the legs, arms or even other parts of the body. The tense feeling and tenderness over the gluteal muscles are marked, and this tenderness may spread to other muscles. The palsy is flaccid; the tendo achillis reflex is usually the first to become diminished, to be followed by the patellar reflexes; later the reflexes are entirely abolished. When vitamin B is added to the diet, the symptoms of B avitaminosis disappear. The appetite improves rapidly; the edema disappears in one to two weeks; the heart action is stabilized, and the sensory and motor disturbances gradually disappear.

The author also conducted an experiment to prove that the alimentary anemia in beriberi is due primarily to a protein deficiency in the diet rather than to a lack of some food factor.

The pathology of B avitaminosis is that of polyneuritis. A segmentation process sets in in many of the fibers of the nerves, followed by wallerian degeneration, just as in the section of a nerve. Animals that show definite palsy but that remain alive for some time show a progression of these changes. Those animals in which the disease runs a rapid course ending in death show no definite segmentation in the nerve fibers, not even in the finest branches. On the basis of these observations it seems probable that the loss of function of the nerves precedes the morphologic change, and it is only after the palsy has existed for some time that the morphologic changes of neuritis ensue.

The degeneration of the muscles in B avitaminosis is distinct in the sense that there appears a definite degeneration of the muscle fibers besides the atrophy. The adrenal becomes definitely enlarged due to hypertrophy and hyperplasia of the cortex and also to stagnation of the blood; the medulla shows no changes. The author never observed in the experimental animals dilatation and hypertrophy of the heart, as it occurs in beriberi in human beings.

The author then reviewed the main features of the four forms of beriberi: (1) the hydropic, (2) the sensorimotor, (3) the atrophic and (4) the acute pernicious. He finally described in detail his observations on the influence of thyroid preparations and iodine on the regeneration of the diseased peripheral nerves, and he came to the following conclusion: "Thyroid preparations in proper dosage accelerate the regeneration of diseased nerve fibers in beriberi. That is the reason why such good results with thyroid preparations were obtained in stubborn cases of palsies of beriberi. Somewhat similar results were obtained through the use of iodine salts. In diseases of the peripheral nerves due to other causes than beriberi, as for instance, in arsenical polyneuritis, Landry's paralysis, etc., we also employed thyroid preparations as well as iodine and we have often noted favorable influences on the paralysis, when the dose was sufficient. That dose is considered proper which causes no loss of weight in the patient."

CAPPER, Philadelphia.

CONGENITAL SOFT SKULL, AND ITS APPARENT ETIOLOGIC RELATION TO INFANTILE RICKETS. E. WIELAND, Ztschr. f. Kinderh. **51**:202, 1931.

Congenital soft skull is a simple, local retardation in the growth of the skull bones, which is due in part to the position of the fetus in utero, as Abels has pointed out, but also to the pressure of the developing brain. The so-called plastic skull is something entirely different. Supra-occipital early softening, on the other hand, found as frequently in hard skulls as in soft ones, is always rachitic. Physiologic or prerachitic craniotabes is nothing more than early rickets, and the oversight of this fact has led to the divergence of figures reported for the incidence of rickets in hard skulls as compared with soft ones, and in certain countries and cities as compared with others. The term prerachitic osteoporosis should be dropped, for every hard skull that is newly found capable of indentation is rachitic. Roentgen and chemical data only gradually follow clinical data, provided that rickets does not heal rapidly, in which case it is occasionally missed. When rickets is present with a soft skull, the diagnosis is easier, but a soft skull does not dispose to rickets.

EMERSON, Boston.

ACID-BASE METABOLISM: THE ABSORBABILITY OF THE RACEMIC LACTIC ACID AND ITS INFLUENCE ON THE ACID-BASE METABOLISM OF THE INFANT. H. FASOLD, Ztschr. f. Kinderh. **51**:247, 1931.

Three infants were fed on a constant diet containing 16.37 Gm. of racemic lactic acid, 1,390 cc. of tenth-normal free acid and 425 cc. of tenth-normal anhydride, a mixture that was completely utilized. The lactic acid caused an acidosis which was made manifest in the increased excretion of ammonia. Simultaneously there was an increase of the output of bicarbonate, which was looked on as a compensatory reduction of the alkali reserve. It seemed paradoxical that when a utilizable organic acid was given, the output of organic acids diminished. The urine was strongly alkaline, the reason for which was studied; it was found that the acidosis was accompanied by a retention of alkali.

EMERSON, Boston.

ISOHEMO-AGGLUTINATION OF HUMAN MILK. K. OSHIDA, J. Pediat. (Tokyo), July 20, 1931, no. 374, p. 909.

A study was made of the agglutination reaction of the mammary secretion before parturition, the colostrum, the first milk, the mature milk and the mammary secretion of infants (witch's milk), against the four types of human red corpuscles. The total number of cases was eighty-nine. The paper includes forty pages of detailed tables, showing the nature of reactions in each set of cases tested. The general conclusions reached are: 1. The agglutination titer of the mammary secretions just before and after parturition is always high. 2. The transitional milk has a lower agglutination titer than the mammary secretions just before or after parturition. 3. The agglutination titer of the mature milk is either negative or lower than that of the colostrum. 4. The milk that agglutinates all four types of human red corpuscles is usually yellow and viscous; this is a temporary reaction and never permanent. 5. The secretions of the mammary glands are not affected by the process of parturition. 6. There is a difference between the right and the left glands in their agglutination reactions. 7. The agglutination reaction of the milk changes with the lapse of time. 8. The agglutination reaction is affected by stasis, the quantity of secretion and the frequency of nursing. 9. No agglutination is demonstrated in the early mammary secretion of the new-born infants. 10. The agglutination power of the human milk against the red corpuscles of type A, type B and type AB varies from day to day just as is the case with the serum. 11. The agglutination titer of the first milk after parturition is higher than that of the serum. 12. The agglutination power of the mature milk is often lower than that of the serum, or even negative. 13. The agglutination power of the milk of mothers whose secretion is scanty is higher than that of normally

secreting milk, and may approach the value of the early milk. 14. The agglutination titer of the serum shows little change after parturition, but that of the milk shows great variation. 15. There is no parallelism between the Wassermann reaction of the milk and that of the serum. 16. The agglutination titer of the milk has no relation to the degree of the Wassermann reaction. 17. There is no special relation between the blood groups and the Wassermann reaction.

KATO, Chicago.

THE DIGESTIBILITY OF MILK PROTEINS; AMINO-ACID METABOLISM IN INFANTS; DRIED MILK. JOSEF ŠEJHAR, Časop. lék. česk. **68**:941 (June 28); 993 (July 5); 1025 (July 12); 1048 (July 19); 1082 (July 26); 1103 (Aug. 2) 1929.

The author reviews the literature and discusses the action of proteins, variation of protein factors in breast and cow's milk, variation in curd formation, digestion, interrelation of amino-acids and their metabolism. The aminonitrogen content of the blood of infants is more labile than that of the adult, decreasing rapidly during starvation, and increasing to a higher level more rapidly after the ingestion of desiccated foods. The urinary aminonitrogen output increases after the intake of desiccated food or after diuresis. The liver performs the synthesis of amino-acids to polypeptides. The aminonitrogen increases twenty minutes after the ingestion of dried foods, and decreases again after forty minutes. The blood aminonitrogen increases more rapidly after ingestion of breast milk, dried milk and buttermilk than after ingestion of boiled fresh cow's milk. The albumin concentration has some effect on the amount and activity of gastric secretion. There is no secondary or latent increase in aminonitrogen after the ingestion of fresh or modified milk, showing that, even though a large curd is formed, albumin-containing mixtures pass quickly through the pylorus. Buttermilk, dried milk and predigested milk are especially valuable in lowered tolerance because of the more rapid absorption. Dried milk may be used over long periods in failure of tolerance for fresh milk, in nutritional disturbances and in mixed feeding, because it contains all the necessary elements (including vitamin C in some brands). Nonskim dried milk was not found useful in diarrhea. The value of a modification of cow's milk protein as a factor in the digestibility of the protein is questioned. Case reports are given showing the usefulness of dried milk in marasmus, dystrophy, spasmophilia, enterocolitis and habitual vomiting. A bibliography is appended.

STULIK, Chicago.

YOGHURT (JA-URT) PREPARATIONS FOR INFANTS. C. SAITZ, Časop. lék. česk. **68**:1037 (July 19) 1929.

Yoghurt is made by the action of veal stomach ferments on milk, and in concentrated form has a caloric value of 1,400 calories per liter. Clinically, it brings nothing new to infant feeding, not obtained by kefir and buttermilk mixtures. It can be fortified with cream, dried milk or other foods. A review of the literature shows that the uses and contraindications for yoghurt are those of any acid milk combination. A few case records are cited to show the value of yoghurt in several types of nutritional disturbance.

STULIK, Chicago.

THE DETERMINATION OF CHLORINE IN SMALL AMOUNTS OF MOTHER'S MILK. B. SJOLLEMA, Nederl. tijdschr. v. geneesk. **75**:3547 (July 4) 1931.

The normal condition and normal function of the breast may be determined from the amount of chlorine present in the product of the glands. In normal breast milk the amount of chlorine is only about one sixth of that in the blood plasma. At the end of lactation and when the breast is infected, the chlorine content of the milk approaches that of the blood plasma. For the determination of chlorine in from 1 to 2 cc. of mother's milk the author has worked out a method that is a modification of van Slyke's (*J. Biol. Chem.* **58**:523, 1923) method for the blood and blood plasma.

VAN CREVELD, Amsterdam, Holland.

CONGENITAL TRACHEOESOPHAGEAL FISTULA: CASE REPORT. V. K. HART, South. M. J. **24**:762 (Sept.) 1931.

A white boy, 1 day old, showed an inability to swallow and choking attacks after nursing. Catheterization and roentgen examination following a barium sulphate enema showed obstruction in the esophagus. There was incomplete closure of the esophagotracheal septum and probably also maldevelopment of this structure, producing the upper blind sac.

SCHLUTZ, Chicago.

MACROGENITOSOMIA AND OTHER DISTURBANCES OF GROWTH AND DEVELOPMENT. W. SPALDING LAURIE, M. J. Australia **2**:100 (July 25) 1931.

At the age of 7 years, a boy had what was diagnosed as acute encephalitis, and later showed precocious sexual and mental development. There was complete optic atrophy of one eye with partial atrophy of the other. Progressive myasthenia and excessive growth of the long bones were noted. There was no disturbance of urinary output or sugar tolerance. The arms showed slight choreiform movements. This is considered to be a pineal gland lesion. The uncertainty of pineal function is admitted, and the variety of symptoms from its disturbance is pointed out. Other disturbances of sexual development and growth, such as primary hypergenitalism, primary hypogenitalism and dystrophia adiposogenitalis, are briefly described.

TENNEY, Madison, Wis.

CONGENITAL OBLITERATION OF THE BILE-DUCTS. ERIC PRITCHARD, Proc. Roy. Soc. Med. **24**:1337 (Aug.) 1931.

A girl, aged 5 months, was first brought to the hospital at the age of 3 months because of progressive jaundice, dark urine and cream-colored stools. The liver was found to be firm and enlarged to three finger-breadths below the costal margin. The lower border of the spleen was 3 inches (7.6 cm.) below the costal margin. The urine contained bile salts and pigments. The stools showed a trace of bile; pigment was present, but much reduced; there were also many fat globules. The Wassermann reaction was negative; the van den Bergh test, positive. Fragility of the blood showed beginning hemolysis in 0.45 per cent saline and none in 0.48 per cent saline. The blood count was normal.

WILLIAMSON, New Orleans.

TWO NEW SYMPTOMS IN OXYCEPHALY OR IN THE PREMATURE CRANIOSYNOSTEOSES AND THEIR PATHOGENESIS. D. GOURFEIN, Arch. d'opht. **48**:112 (Feb.) 1931.

The author calls attention to two new ocular symptoms in this type of malformation. In addition to exophthalmos and optic atrophy, which are the most common ocular abnormalities, he has observed three cases in which bilateral ptosis and paralysis of convergence were present, and he abstracts a fourth previously reported by Mirimanoff in 1924. He discusses the theories suggested to account for these conditions, and expresses his belief that although they may have a common cause, they are probably not directly the result of the cranial deformity.

MARLOW, Syracuse, N. Y.

ANATOMIC CONSIDERATIONS OF CERTAIN CONGENITAL MALFORMATIONS OF THE BILIARY PASSAGES. MAURICE PÉHU and PAUL GIRARD, Rev. franç. de pédiat. **7**:205, 1931.

This article consists of a long discussion of the gross anatomic and histologic changes that take place in the liver following obstruction to the outlet of bile. There is also some discussion as to the development of various types of occlusion of the bile duct. The authors report two cases, in one of which the patient showed

jaundice at birth and died at the age of 2 months. Autopsy showed absence of the bile duct and ulceration of the duodenum, together with cirrhotic changes of the liver. The other patient developed jaundice at 11 months of age, and died four months later. Autopsy revealed a fibrous tract extending from the liver to the duodenum instead of a normal bile duct. It is supposed that there must have been some inflammation preceding the development of the condition.

LESLIE, Evanston, Ill.

A CASE OF ACHONDROPLASIA. VICTORIO CHALLIOL, Arch. gen. di neurol. e psichiat. **11**:349, 1930.

A patient, aged 13, 112 cm. tall and weighing 30.6 Kg., presented a typical picture of achondroplasia. Photographic and x-ray plates were demonstrative of the condition. There was moderate mental deficiency. The patient also had a spina bifida occulta. Neurovegetative tests gave a distinctly vagotonic response: a high basal metabolism (+ 32) and a low p_H of the urine (6.2). The Wassermann reaction of the blood was negative. The author emphasizes the signs of endocrino-vegetative disturbance (hyperthyroidism with vagotonia) presented by his patient. He regards this disturbance as one possible factor in the production of the syndrome of achondroplasia.

YAKOVLEV, Palmer, Mass. [ARCH. NEUROL. & PSYCHIAT.].

A CASE OF CONGENITAL ABSENCE OF THE SACRUM. M. SALVAT ESPASA, But. Soc. Catalana de pediat. **1**:48 (July) 1928.

Some of the comparatively few cases of congenital absence of the sacrum and coccyx are reviewed, and what is believed to be the first typical case in the Spanish medical literature is presented. Outstanding symptoms are a collapse of the vertebral column in the pelvic region and atrophy of all the muscles innervated by the sacral plexus. Hence, there is a marked disproportion between the upper and the lower divisions of both the trunk and the extremities. There is incontinence of urine and sometimes of feces. The Achilles reflex is absent, and there is a perianal hypesthesia. Rectal examination is the surest method of clinical confirmation, while roentgenograms reveal the exact deformity. Although frequent in the cases reviewed, no known accident or pathologic process occurred during pregnancy. The Wassermann reaction was negative, and the ancestral history revealed no similar defect.

WATSON, Elmhurst, Ill.

ARACHNODACTYLIA. H. WEVE, Arch. f. Augenh. **104**:1 (Jan.) 1931.

The author gives a sketch of arachnodactylia or dolichostenomelia based on a series of his own cases as well as a review of the literature. He reports twenty-three cases from six families. These are added to the sixty cases already reported in the literature. The clinical entity is apparently more common in Holland than the literature would lead one to believe. Women are not more frequently affected than men. The disease is essentially familial, and this becomes especially apparent if one includes the arrested cases, the so-called formes frustes.

It is an inherited character and essentially dominant. About half of the children of one family are affected, but usually only a single branch of a large family. The cause of this incomplete dominant mode of inheritance cannot be accounted for. Basal metabolic studies made on these cases suggest that the syndrome is a congenital form of mesodermal dystrophy. The classic picture of the disease consists essentially in an abnormal length and thinness of the extremities, especially the hands and feet. In the well marked cases all the bones of the arm are abnormally long and the abnormal proportions seem to increase from the shoulder to the fingers; in other words, the disease can be most easily detected by a glance at the hands. The muscles show no paralyses or appearance of

degeneration. Occasionally contractures of the joints are met with, from which the disease gets its name, the fingers becoming like spider feet. In from 40 to 50 per cent of these cases there are bilateral congenital ocular anomalies. For the most part these consist in luxation or subluxation of the lens. As a consequence of the more spherical form of the subluxated lens there may develop a high myopia, or, if the edge of the lens lies below the pupil opening, a marked hypermetropia may be present.

ADLER, Philadelphia [ARCH.OPHTH.].

CHONDRODYSTROPHIA CALCIFICANS CONGENITA AS AN ABORTIVE FORM OF CHONDRODYSTROPHY. CARL HÜNERMANN, Ztschr. f. Kinderh. **51**:1 (May) 1931.

The first case of chondrodystrophia calcificans congenita was reported by Courade in 1914; two more have been reported since then, and a third is described by Hünermann. A child born at the eighth month of pregnancy was admitted to the hospital at the age of 3 weeks because of failure to gain. The striking thing about the baby was her form, which seemed like that of a child with chondrodystrophy, the soft parts being overdeveloped, especially those of the upper part of the leg. The upper part of the right leg was shortened, and in roentgenograms a peculiar calcification, in flecks as if sprayed, could be seen in the epiphyses and in the bones laid down in cartilage. Roentgen examination of the whole skeleton, however, gave no typical signs of chondrodystrophy, nor were the proportions characteristic. At the end of the second year the child showed overdevelopment of the musculature, but it was not so startling as at first. The right leg was 1.5 cm. shorter than the other, and the deposits of calcium were gradually disappearing.

The case, then, did not seem to be one of chondrodystrophy, until it was compared with that of Courade, which it resembled closely and which was shown by microscopic study to be one of abortive chondrodystrophy because of the complete laying down of endochondral bone in the presence of undisturbed perichondrial ossification and because of stripes in the periosteum, in several epiphyses, which are characteristic. The deposits of calcium, histologically, are bone nuclei, and are not an independent observation, but are peculiar to this form of chondrodystrophy. The shortened right leg is an expression of localized chondrodystrophy.

EMERSON, Boston.

FETAL ERYTHROLEUKOBLASTOSIS. L. SALOMENSEN, Ztschr. f. Kinderh. **51**:181 (June) 1931.

Five cases of hydrops congenitus with fetal erythroleukoblastosis are described, one of them with the results of intravital examination of the blood which did not confirm the suspicion that a high grade anemia had previously existed with this condition. In fifty-two normal newly born babies, the liver and spleen were studied histologically as to their content of iron pigment. The hemosiderosis in hydrops congenitus was not so different from that found in normal babies that a conclusion could be drawn as to a previous primary destructive anemia. There is a close relation between hydrops congenitus and icterus congenitus gravis familiaris, as evidence for which is the following history of a family: the parents were healthy, as was the first child; the second child had icterus congenitus gravis, the third child hydrops congenitus with erythroleukoblastosis and the fourth child icterus congenitus gravis. There can be demonstrated in apparently normal, full term newly born babies, an erythroleukoblastosis of the same degree as in hydrops congenitus and icterus congenitus gravis. It might be justifiable, perhaps, to set up as a special fetal group of diseases a fetal erythroleukoblastosis caused by a primary constitutional lack in the hematopoietic system, this group to include hydrops congenitus as well as icterus congenitus gravis.

EMERSON, Boston.

ROENTGENOLOGIC DIAGNOSIS OF FETAL DEATH DURING PREGNANCY. FRANK SPAČEK, Časop. lék. česk. **68**:1013 (July 12) 1929.

Of 400 fetuses examined roentgenologically, 25 were found to be stillborn. The diagnosis can be made quite readily after four months and only rarely during the third month. Postmortem changes take place more rapidly in the younger fetus. An early sign is the increased curve in the spine and later almost a circle formation. Another sign is the displacement of the cranial plates. This may go on slowly in the presence of an increase of amniotic fluid. In transverse and oblique presentations the increased cranial pressure produces rapid changes in the cranial contour. Of the 25 stillborn fetuses studied, only 1 was in an advanced stage of maceration.

STULIK, Chicago.

THE EMBRYOLOGIC DEVELOPMENT OF CANALICULI LACRIMALIS IN FACIAL FISSURE. HOLGER EHLERS, Acta ophth. **8**:305, 1930.

The author describes a case of bilateral oblique facial fissure with upward palpebral coloboma, and considers the theories proposed for this anomaly. The embryologic relations involved in the formation of the face and the primordial development of the nasolacrimal ducts are discussed. From this study he concludes that the primordial development of the nasolacrimal canals starts from the very point where the primary oblique facial fissure has its origin, and the canaliculi lacrimalis originates from the upper end of the ducti nasolacrimalis primordium. He notes that Fleischner believes that both canaliculi in mammals are derived from the upper constricted end of the duct and grow into the protuberance of the eyelids, until they come in contact with the epithelium of the lid margin. The case in question corroborates the alleged origin of the canaliculi from the lacrimal tissue rather than from the epithelium of the margin of the lid.

YUDKIN, New Haven, Conn.

ARACHNODACTYLIA. P. R. MICHAËL, Nederl. tijdschr. v. geneesk. **75**:262 (Jan. 10) 1931.

A case of arachnodactylia is described in a girl of 9 years. The disease is regarded as a constitutional anomaly, and its symptoms, in analogy to those described by former investigators, are opposed to those of chondrodystrophy.

VAN CREVELD, Amsterdam, Holland.

Diseases of the New-Born

TETANY ACCOMPANIED BY HYPERPYREXIA AND VOMITING IN THE FIRST DAYS OF LIFE. M. H. BASS and S. KARELITZ, J. A. M. A. **97**:1372 (Nov. 7) 1931.

It has been assumed that tetany does not occur in the new-born infant. Three cases are presented in new-born infants who manifested a clinical picture of tetany. These infants became extremely ill during the first days of life, with vomiting, a markedly distended abdomen, a high fever, dysphagia and signs of great nerve irritation — Chvostek's sign, carpopedal spasm, hoarse cries and repeated convulsions. Calcium given intravenously and hypodermically resulted in prompt recovery. The cause could not be ascertained, but the profuse vomiting suggests the possibility that the condition was of gastric origin, secondary to vomiting.

BONAR, Salt Lake City.

THE DIAGNOSIS OF INTRACRANIAL HEMORRHAGE IN THE NEW-BORN. CLIFFORD G. GRULEE, New York State J. Med. **31**:1032 (Aug. 15) 1931.

The diagnosis of intracranial hemorrhage is not as easily made as many have thought. Many nervous disorders attributed to this condition are more apt to be due to some congenital brain defect. Probably the diagnosis of intracranial hemorrhage should include cerebral edema, fracture of the skull, cerebral congestion and

anemia because it is difficult and frequently impossible to differentiate between these conditions. The symptoms, including lethargy, refusal to nurse, a whining cry and coma, may be present in other conditions. The physical findings must also be very carefully considered if one is to arrive at the correct diagnosis. Focal signs are practically absent, and one cannot depend on eyeground examinations for a positive diagnosis. While convulsions in the new-born may be due to other causes, probably the majority are due to cerebral hemorrhage. Bloody spinal fluid must be carefully examined, especially for crenated cells, because it is not easy to rule out the bloody fluid that may be caused by the spinal puncture itself. Xanthochromatic fluid is more apt to be due to icterus. Not all cases of chronic spastic paralysis in later life are due to intracranial hemorrhage. Congenital brain defects or encephalitis may have caused cases of Little's disease that have been attributed to intracranial hemorrhage. "We are at present in no position to make a diagnosis of intracranial hemorrhage in the new-born in the majority of instances."

AIKMAN, Rochester, N. Y.

A METHOD OF STUDY OF INTRACRANIAL HAEMORRHAGE IN THE NEW-BORN INFANT. F. M. B. ALLEN and H. I. MCCLURE, Arch. Dis. Childhood **6**:98 (April) 1931.

The authors described an apparatus and a method for injecting into the carotid artery an emulsion that makes the vessels of the brain visible in roentgenograms. A study can then be made of the size, site and number of intracranial hemorrhages. The advantages are that permission for autopsy is unnecessary, the technic is simple, and there is accurate localization by stereoscopic plates in a permanent pictorial record.

KELLY, Milwaukee.

LOCALIZED FAT NECROSIS OF THE NEW-BORN INFANT. KARL LINSER and SOPHIE PÖTSCHKE, Dermat. Ztschr. **62**:53 (Sept.) 1931.

Four cases of fat necrosis of the new-born infant are reported. The condition is due most frequently to trauma, and consists in a necrosis of fat cells with splitting up of the released fat into fatty acids. These fatty acids act as irritants on the reticulo-endothelial system to produce an inflammatory granuloma of the foreign body type. In contrast to the course in adults, the lesions do not tend to break down, rarely calcify and disappear without scar formation. The authors do not consider the condition rare. It appears in the literature under various names.

TAUSSIG, San Francisco [ARCH. DERMAT. & SYPH.].

THE CAPILLARY RESISTANCE OF PREMATURE AND NEW-BORN INFANTS. WERNER BERNFELD, Monatschr. f. Kinderh. **51**:1, 1931.

By means of a specially constructed suction apparatus applied to the skin, the author determined the amount of negative pressure necessary to produce capillary hemorrhage. He reviews the work of other investigators and disagrees with the conclusions expressed by many of them. For instance, he cannot confirm Yllpö's observation that there is a relation between birth weight and a tendency toward hemorrhage, nor does he agree with Bayer that this tendency depends on the course of labor. He questions whether there is an increased tendency to bleeding during the first four days. He does agree with Yllpö that increasing resistance of the blood vessels is definitely related to the age of the fetus. However, the capillary resistance seems somewhat less during the first six months of life than at the time of birth. Bernfeld confirms Yllpö's observation that premature infants who will die in a short time show an increased tendency toward bleeding, this tendency increasing, the nearer they are to death. The administration of calcium gluconate was found to have no effect. The negative pressure necessary to produce hemorrhage varied from 200 to 600 mm. of mercury.

GERSTLEY, Chicago.

THE QUESTION OF ICTERUS NEONATORUM. S. KRAMAZTYK, Ztschr. f. Kinderh. **51**:273, 1931.

By an early examination of the blood and urine for biliary color substances the diagnosis of icterus neonatorum gravis familiaris can be made, and by a timely transfusion or injection of blood this disease can be cured.

EMERSON, Boston.

THE REGULATION OF BLOOD SUGAR IN PREMATURE BABIES. F. HAASS, Ztschr. f. Kinderh. **51**:400, 1931.

Hypoglycemia to a considerable degree was found in premature infants with a subnormal temperature, and the blood sugar curve followed closely the speed of reaction-temperature rule of Kanitz. By comparison with hypoglycemia produced experimentally, or in decompensation of the heart, it was apparent that the cause was a harmful influence on the vegetative nervous system and, secondary to this, a retardation of glycogenolysis. In contrast to van Creveld, Haass sees in this form of hypoglycemia only a proportionately small, partial appearance of functional immaturity. It is to be considered that even in premature babies the regulation of temperature is not a simple chemical reaction but a complicated working together of the nervous and endocrine systems, which points to a considerable capacity for regeneration and compensation after severe injury from the lowering of the temperature.

EMERSON, Boston.

Acute Infections

TOXOID AS AN IMMUNIZING AGENT IN DIPHTHERIA. HARTZELL HARRISON RAY, Am. J. M. Sc. **182**:251 (Aug.) 1931.

The immunization of 358 children with toxoid is reported. Of 333 who received 2 cc., 98 per cent gave negative Schick reactions, and of 25 who received 1 cc., 84 per cent were immunized. Two injections of 1 cc. each, ten days apart, were given. Children under 8 years of age react less frequently than those over this age limit. Local and general reactions may be seen. Toxoid is considered safe, reliable and efficient in the immunization of children against the ravages of diphtheria.

HENSKE, Omaha.

CURRENT PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **46**:2093 (Sept. 4) 1931.

For the period of July 19 to Aug. 15, 1931, there was an epidemic of poliomyelitis in the Middle Atlantic and New England states. The peak in New York City was 591 cases in the week of August 8. There were only 512 the following week. There was a slight increase in the South Central and Western regions. There was also a slight increase in meningococcus meningitis and scarlet fever, but a decrease in measles, smallpox and diphtheria. The average death rate was 10.3 per thousand as compared with 11.0 for the same period in 1930.

SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **46**:2357 (Oct. 2) 1931.

For the period of Aug. 16 to Sept. 12, 1931, the peak of the poliomyelitis epidemic seemed to have been reached during the week ending September 12; 1,160 cases were reported as compared with 1,370 for the preceding week. So few cases have been reported in the Southern Mountain and Pacific states that it cannot be said whether or not their peak has been reached. Scarlet fever, diphtheria, meningo-

coccus meningitis and influenza showed a slight increase. The incidence of measles, smallpox and influenza was lower. The general mortality was 9.9 per thousand, whereas it was 10.6 for 1928 and 1929.

SANFORD, Chicago.

ON THE INCIDENCE OF RHEUMATIC FEVER. FRANCIS BACH, Brit. J. Child. Dis. **28**:198 (July-Sept.) 1931.

Rheumatic fever is commonest in Great Britain, Germany, France and North America. In Holland and Scandinavia it is less common. The author cites some of the figures appertaining to the incidence of organic heart disease in Great Britain and various other north European countries. He found that the clinical picture of rheumatic heart disease was similar in all these countries. Coburn's studies are cited in which he concluded that Streptococcus haemolyticus is an important factor in the production of rheumatic states. It is possible that the "rheumatic state" or diathesis is dependent on certain familial and environmental factors, and that in these susceptible persons a certain organism, possibly Streptococcus haemolyticus, may set up a tissue reaction, which manifests itself as the clinical picture of "rheumatismus infectiosus specificus" or rheumatic fever.

LANGMANN, New York.

THROMBO-PHLEBITIS MIGRANS COMPLICATING SCARLET FEVER. J. B. ELLISON, Brit. J. Child. Dis. **28**:207 (July-Sept.) 1931.

Two cases are cited, both in boys, aged 6 and 10½ years, respectively, who were in the same ward at the same time, being separated by one bed. Following an attack of scarlet fever the first boy developed cervical adenitis, nephritis and bilateral otitis media and mastoiditis, and was operated on. At operation a hemolytic streptococcus was cultured from the mastoid wound. Both boys developed a severe painful swelling of both lower extremities which was ascribed to temporary obstruction of both external iliac veins. The condition subsided gradually and both patients made complete recoveries.

LANGMANN, New York.

THE PHASES OF HAEMOPHILUS PERTUSSIS. P. H. LESLIE and A. D. GARDNER, J. Hyg. **31**:423 (July) 1931.

This is an investigation of the serologic composition and variation of Hemophilus pertussis. Analyses of thirty-two strains were made with reference to agglutination tests. Four well marked agglutination groups, called phases I, II, III and IV, were found. Strains from France, Denmark and America were also studied. Most of them, especially the fresh ones, fell into phase I. Of the authors' strains and those from Denmark, four were toxic to guinea-pigs. Only one of the twelve other strains tested was toxic. In the American classification "B" proved to correspond absolutely to the authors' phase III, and "A" with phase IV. The technic of cultivation, absorption tests and agglutination tests is given. The interrelationship of the different phases is shown, as is the fact that by certain changes in the character of the mediums a single colony can produce, in turn, all the antigens characteristic of the four phases. This transformation is also largely remissible.

The authors believe that phases I and II correspond to the smooth or pathogenic form of other bacteria; phases III and IV, to the rough, relatively harmless saprophytic form. Cultures of phase I are from twenty to thirty times more toxic to guinea-pigs than are those of phases III and IV. Death was purely toxic, and there was no multiplication of the culture within the guinea-pig. In immunity experiments, those first immunized with a vaccine of killed viable phase I organisms survived when given phase I organisms, while the controls and all those protected with phase III living vaccine died when given phase I organisms.

A commercial prophylactic "B" pertussis vaccine was found to be serologically in phase III. In tests similar to the foregoing, it and phase IV vaccine failed to protect experimental animals. Vaccines from phase I organisms are the only ones that this work suggests as being of value.

JANNEY, Milwaukee.

THE PHOSPHOLIPOIDS IN THE BLOOD SERUM OF CHILDREN WITH DIPHTHERIA, ESPECIALLY WITH POSTDIPHTHERITIC PARALYSIS. C. COCCHI, Riv. di clin. pediat. **29**:581, 1931.

The method of Whitehorn (*J. Biol. Chem.* **67**:133, 1924) was used to measure the amount of phospholipoids in the blood. Nineteen children with diphtheria and six control cases — two showing nondiphtheritic angina — were used in this study. The amount of phospholipoids in the blood of children with diphtheria is definitely small; it is even smaller in the cases of paralysis. During convalescence, it becomes very large.

HIGGINS, Boston.

ANTIVARIOLAR VACCINATION IN THE TREATMENT FOR PERTUSSIS. F. A. CONI BAZÁN, Arch. argent. de pediat. **2**:42 (Jan.) 1931.

The author comments on an article written by Dr. Schiavone on antivariolar vaccination in the treatment for pertussis. He also reports the results of his own study of thirty-three patients with pertussis. He concludes that there is no specific treatment for pertussis. He believes that the fact that the virulence of the disease varies with different epidemics and that the disease so frequently runs a very mild course is responsible for the apparent success of the innumerable methods of treatment, including the one referred to by Schiavone, namely, antivariolar vaccination.

SCHLUTZ, Chicago.

THE PREVENTION OF CHILDREN'S CONTAGIOUS DISEASES. BRAVO FRIAS, But. Soc. Catalana de pediat. **1**:5 (July) 1928.

The author believes that too much attention is being paid to disinfection of furniture when the real danger lies in the nose and throat. He takes up each contagious disease in great detail, giving the following suggestions for prophylaxis for each: For syphilis he advises complete clinical examination plus Wassermann tests of parents and wet-nurses, as the Wassermann reaction is unreliable in the new-born infant. In tuberculosis he stresses the importance of obligatory reporting of all cases, isolation of carriers and of children of tuberculous parents. In a group of institutionalized new-born infants vaccinated by the Calmette method, there was a 1.1 per cent mortality from tuberculosis in 358 children vaccinated as compared with a 3.8 per cent mortality in 880 who were not vaccinated. In measles he prefers the sero-attenuation rather than the seroprevention method using convalescent serum. In scarlet fever he finds that Dick serum is effective in cases in which the extinction phenomenon is present, but not in other cases. In whooping cough he finds prophylactic vaccination useless. He recommends the culture plate for early diagnosis.

WATSON, Elmhurst, Ill.

ANTIDIPHTHERIA VACCINATION. J. A. ALONSO MUÑOYERRO, But. Soc. Catalana de pediat. **1**:18 (July) 1928.

Fifteen hundred patients were inoculated with anatoxin, and 98 per cent became immune after three doses. The innocuousness of anatoxin is emphasized.

WATSON, Elmhurst, Ill.

METHOD OF SELECTING ANIMALS FOR IMMUNIZATION WITH THE TOXIN OF DIPHTHERIA. E. SAVINO, Rev. Soc. argent. de biol. **6**:482, 1930.

It is well known that each animal has its own individual curve in the production of antitoxin when immunized with diphtheria toxin. At the termination

of the course some animals are worthless so far as the antitoxin content is concerned as well as for other serologic work. Each week the author measures the antitoxin content of the blood of each animal by the flocculation method of Ramon. From tables that he has devised he is able to predict whether or not the animal will be of commercial value at the end of the fourth injection.

HARRISON, Iowa City.

MICROCOCCUS TETRAGENUS AS A CAUSE OF SEPSIS IN INFANCY. E. KRAMÁR, Arch. f. Kinderh. **92**:248 (Feb. 13) 1931.

A child, 3½ months old, had a septic temperature of 40 C. (104 F.) for three weeks. The Wassermann and tuberculin tests were negative. A blood culture showed colonies of Micrococcus tetragenus. An intravenous injection of acriflavine and a transfusion were given, but improvement began only after the intravenous injection of resorcinol.

SANFORD, Chicago.

THE PRESENT STATUS OF THE SCARLATINA QUESTION. W. KNÖPFELMACHER, Wien. klin. Wchnschr. **43**:1447 (Nov. 20) 1930.

Knöpfelmacher reports that the typical scarlatina exanthem is well known: the diffuse, dark erythema of the face with circumoral pallor, the macular dark erythematous patches on the trunk with distribution of the single maculae around the follicles and the extension to the extremities. Besides, the typical angina is characterized by reddening of the uvula and palatine arches and edematous infiltration. Coating is often absent; the tonsils may be free. Adults frequently show only this angina (scarlatina without exanthem), while a child has scarlatinal angina. Another atypical form is the relatively benign scarlatina miliaris: the intensely dark red exanthem shows small vesicles here and there, especially around the follicles, but sometimes also more diffusely. Besides the typical exanthem, one occasionally sees a diffuse spread of nodules, recalling papules or wheals. Of practical importance is toxic scarlatina: The individual points coalesce into a diffuse erythema; the color is deep purple or Bordeaux red; on pressure the skin shows a rather strong yellow discoloration. A very high temperature, a very rapid pulse rate, loss of consciousness, diarrhea, constant vomiting and apathy indicate a poor prognosis. Septic scarlatina, on the other hand, shows a considerable tendency toward swelling of the lymph glands, rheumatic complaints, articular effusions, peritonsillitis and retropharyngeal abscess. Streptococci are found in the blood. Icterus is common. A necrotizing angina is present, with a thin but tenacious membrane. The necrotizing inflammation occasionally spreads to the nasopharynx, the mucous membrane of the cheek, the tongue and even the esophagus. A thin nasal mucus drips almost continuously and ulcerates the skin of the lip. Frequently the cervical glands suppurate. Mild cases of scarlatina with an insufficiently marked exanthem are recognized by the typical angina and the swelling of the skin follicles, particularly when there is a slight erythema present. In the light exanthems which often disappear after a few hours, the extension, color and distribution around the follicles are of particular value.

A. F. ABT, Chicago.

LATE ICTERUS IN SCARLET FEVER. L. ROSENWALD, Ztschr. f. Kinderh. **51**:255, 1931.

In 18, or 0.78 per cent, of 2,313 cases of scarlet fever, icterus occurred during the second to the twelfth week. There was an increase of this complication last year which ran parallel with an increase of icterus simplex. Late icterus is independent of the severity of scarlet fever and other complications and of convalescent serum. It is necessary to exclude the possibility of paratyphus fever.

EMERSON, Boston.

BACILLARY DYSENTERY (SONNE) AT AMSTERDAM. A. C. RUYS, Nederl. tijdschr. v. geneesk. **75**:1909 (April 11) 1931.

Bacillary dysentery of a mild character occurs endemically in Amsterdam, principally caused by the so-called Sonne or Kruse E bacillus. In exceptional cases, Flexner's dysentery bacillus is found.

VAN CREVELD, Amsterdam, Holland.

Chronic Infections

THE LEUKOCYTIC REACTION IN TUBERCULOSIS OF INFANCY AND CHILDHOOD: BLOOD STUDIES WITH THE SUPRAVITAL TECHNIQUE. CARL H. SMITH, Am. J. M. Sc. **182**:221 (Aug.) 1931.

The blood picture of a tuberculous child or infant may be accurately correlated with the activity of the tissue lesion. The supravital technic, allowing examination of cells in their living state, was used. The activity picture is made up as follows: an increased white cell count, an elevation of polymorphonuclear neutrophils and monocytes, a drop in the number of eosinophils and lymphocytes and a rising monocyte-lymphocyte ratio. Stimulated monocytes and epithelioid cells are observed only in the most acute cases. A reversion toward the normal blood picture is found in the healing and resistant stages. The monocyte-lymphocyte ratio is stressed, as an idea of the progress of the disease may be derived from a numerical comparison of this kind, when one also considers the other white blood cells.

HENSKE, Omaha.

THE ANTISYPHILITIC ACTION OF THE MALARIAL PARASITE IN OTHER THAN CENTRAL NERVOUS SYSTEM SYPHILIS. CHARLES C. DENNIE, HARRY M. GILKEY and SIDNEY F. PAKULA, Am. J. Syph. **15**:320 (July) 1931.

The authors state that the antisyphilitic action of the malarial parasite has not been established. Up to the present time the use of antimalarial parasite treatment has been limited to certain types of syphilis of the central nervous system. The benefit of such treatment cannot be denied by any one who is familiar with the procedure. Although the symptomatology is altered after malarial treatment, in a great many cases the serology remains but slightly changed. In order to prove its benefit, one must actually see by the aid of the microscope or roentgen study the actual disappearance of hyperplastic syphilitic tissues. It is natural to assume that if there is an eliminating or retarding effect on the course of dementia paralytica there is no reason why the same parasite should not have the curative effect on the constructive syphilitic processes in the bone, skin, eye and vascular system.

The authors then make the statement that the purpose of this paper is an attempt to prove that malaria as given to the syphilitic patient has a definite antisyphilitic reaction, no matter where the process is located. They selected two types of cases on which to experiment, one group composed of patients who had had no treatment and the other of patients in whom treatment by other methods had been unsuccessful. A report is then made of four cases of interstitial keratitis, one case of hyperplastic bone disease, one case of joint disease and one case of malignant skin disease, all the patients being treated with malarial parasites. In a boy, aged 11 years, the left elbow was affected. A roentgenogram showed marked hyperplastic thickening of the entire lower end of the humerus, which was encased in a wedge-shaped cylinder of new bone. The roentgenogram was considered typical of syphilitic bone disease. In October, 1929, he was inoculated with malaria. At the end of eleven days, after definite evidence of active malaria, he was given quinine treatment. Eight weeks afterward the limitation of motion was entirely gone, and the boy was practically well. A similar case, more or less analogous in many respects, was that of a girl, aged 8 years, with chronic arthritis of the left knee and a severe conjunctivitis of the left eye. Three weeks after

similar treatment she was walking with but a slight limp, and the eye seemed to be perfectly clear. A girl, aged 14 years, showed a severe interstitial keratitis. Treatment was begun on July 18, 1930, and on September 12 the ophthalmologist reported unusual improvement for such a short period. By January, 1931, there was no evidence of the keratitis. Another girl, aged 14 years, showed practically the same picture. None of these patients had had syphilitic treatment. A girl, aged 8 years, had been treated for a year in order to prevent keratitis in the course of her syphilis; in spite of this she had a severe attack. She was inoculated on Jan. 27, 1931, and given malarial treatment in due course; five weeks later all symptoms of keratitis had disappeared. A 29 year old man had malignant dermatitis of a nodulo-ulcerative type with a superimposed arsenical dermatitis and hepatitis. Antisyphilitic treatment by malarial inoculation was equally effective in this case.

ROYSTER, University, Va.

BISMUTH IN THE TREATMENT OF SYPHILIS. CARROLL S. WRIGHT, Internat. Clin. **2**:214 (June) 1931.

Bismuth has been accepted as a powerful weapon in the fight against syphilis, therapeutically inferior to the arsenobenzenes, but superior to mercury in its therapeutic value and its lower toxicity. The vehicle in which it is given is more important than the actual amount of bismuth given. Water-soluble preparations seem most efficacious. Intravenous therapy is contraindicated. In primary syphilis spirochetes cannot be found by gland puncture after three injections. Bismuth is the drug in visceral syphilis and is apparently not hepatotoxic. There are practically no ill effects when it is given to children, and there is little local pain. In 25,000 injections given at the Graduate School of the University of Pennsylvania, over a period of nine years, there has been no severe untoward effect.

MILLER, South Bend, Ind.

OBSERVATIONS ON THE USE OF B.C.G. VACCINE IN NASHVILLE, TENNESSEE. JOHN OVERTON, South. M. J. **24**:878 (Oct.) 1931.

If B C G vaccine is prepared by a laboratory technician who will follow Calmette's instructions and employ every safeguard, its use is without danger. Patients inoculated by the intradermal method will show allergy in almost 100 per cent of the cases. The protection given and the length of time it lasts are still undetermined. There seems to be a high degree of protection. This method is applicable to groups in schools, institutions, colleges, nursing and medical schools, factories and the army and navy, as well as in individual families.

SCHLUTZ, Chicago.

CONGENITAL TUBERCULOUS INFECTION. C. MONCKEBERG, Rev. de la tuberc. **12**:481 (April) 1931.

While the complexity of the problem of congenital tuberculosis precludes the possibility of definitive statements on many points, laboratory and clinical experience warrants the following conclusions at the present time: 1. Hereditary tuberculous infection is an incontestable fact. It may manifest itself in three forms: (*a*) infection of the fetus by the passage of a filtrable virus through the placenta, (*b*) a bacillary infection without lesions and (*c*) a bacillary infection with anatomic changes. These three forms, however, are not distinct types of hereditary infection but successive stages in the evolution of one pathologic process. 2. As would be suspected, infection with the filtrable virus occurs most frequently, since the virus is able most readily to pass through the placental villi. It may, however, coexist with bacillary infection, and under the influence of as yet unknown factors, further evolution may result in the development of anatomic tuberculosis. 3. The primary state of infection with the ultramicroscopic virus is equivalent to a period of incubation, preceding the development of specific lesions. Such infection may

manifest itself in the infant as a cachexia or state of malnutrition, and may even eventuate in death. On the other hand, the infection may remain latent, localized in the lymphatic system. 4. If the condition of the placenta allows of the mixture of maternal and fetal blood, bacillary and anatomic tuberculosis may readily occur. The protective factors inherent in the placenta are efficient in defending the infant from this accident except in comparatively rare instances.

The main points in the author's thesis are: The passage of a filtrable virus through the placenta to the fetus has been demonstrated. These filtrable elements are able to regenerate in the animal organism, acid-resistant bacilli capable of producing anatomic tuberculosis. The factor determining the morphologic state of the germ at the time of birth is the age of the infection, the length of time that the fetal organism has harbored the virus. Congenital tuberculosis may occur as an evolutional process, consisting of infection with a filtrable virus, a prebacillary stage, the regeneration in the organism of acid-fast bacilli and, finally, the development of anatomic tuberculosis.

SMITH, Ogden, Utah.

THE HINTON REACTION IN THE DIAGNOSIS OF SYPHILIS. ROMIRO DANTE POLICARO, Clin. pediat. **13**:587 (July) 1931.

The author describes in detail the technic of the Hinton test for the diagnosis of syphilis, and adds a comparative study of this test and the Wassermann test. The study totaled 305 tests in two groups of subjects, one known to have syphilis and the other known to be nonsyphilitic. In 80 per cent of the tests there was complete agreement between the two reactions, while in 5 per cent the Hinton reaction was more sensitive. This superior sensitiveness was noted in cases of long standing in which treatment had been insufficient. The resulting definite conclusions were summarized as follows: 1. The Hinton reaction is more sensitive than the Wassermann, and is particularly valuable in establishing a diagnosis in cases of latent syphilis. 2. The Hinton reaction possesses a notable specificity in the serodiagnosis of syphilis, because no positive reaction was obtained in cases known to be nonsyphilitic. It was also noted that as the positive cases improved clinically under treatment, the Hinton reaction diminished in intensity, and finally disappeared parallel to the Wassermann reaction. 3. Because of the simplicity and quickness of execution, as well as the superior sensitiveness over the Wassermann reaction, and more particularly because of the simple and reliable reading of the reaction, the Hinton test should be applied with the Wassermann test in order to establish the diagnosis of syphilis more conclusively. This is especially true in cases of latent syphilis.

SIGNORELLI, New Orleans.

SCLERODACTYLY ("AKROMIKRIE") AND SYPHILIS. G. J. UMANSKY, Dermat. Wchnschr. **92**:880 (June 13) 1931.

A woman, aged 25, who had congenital syphilis, was observed. She presented general underdevelopment, with thinning of the joints of the end-phalanges of the extremities, small maxillae, nose and lips, acrocyanosis, dystrophy of the nails, a subnormal temperature and a small hypophysis. Antisyphilitic therapy resulted in general improvement.

TAUSSIG, San Francisco [ARCH. DERMAT. & SYPH.].

THE CHOICE OF CHILDREN ADAPTED TO TREATMENT IN A SANATORIUM FOR TUBERCULOSIS. A. REICHE and EVA ENDRES, Gesundh. fürs. f. d. Kindesalt. **6**:179 (June) 1931.

The authors again call attention to the fact that the value of the tuberculin reaction is not yet common property of the general practitioner. Fifty per cent of the applicants for treatment at a tuberculosis sanatorium had never been tested for tuberculin sensitivity. Twenty per cent of the children were found to be entirely free from any tuberculous infection.

REICHLE, Cleveland.

BACILLEMIA IN GENITO-URINARY TUBERCULOSIS. R. LICHTENSTERN, München. med. Wchnschr. **78**:471 (March 20) 1931.

The diagnosis of a recent tuberculous infection of the genito-urinary tract is a difficult problem. Frequently it is not possible to find tubercle bacilli in the urine, and it requires many weeks to obtain results from animal inoculations. By using Löwenstein's technic for culturing tubercle bacilli from the urine definite data were obtained more quickly than by animal inoculation. In addition, Löwenstein's method for culturing tubercle bacilli from the blood was helpful in making early diagnoses in genito-urinary tuberculosis. Lichtenstern cultured the blood from twenty-seven patients with various nontuberculous lesions of the genito-urinary tract. These control cultures were negative. In three cases of suspected tuberculosis of the upper urinary tract the cultures of the blood were positive for tubercle bacilli, even though no bacilli could be found in the urine at that time. However, several weeks later tubercle bacilli were present in the urine.

Blood cultures were then used to determine when a patient was cured after an operation for tuberculosis of the genito-urinary tract. Many patients have a fever for one or two weeks following nephrectomy. During this time Lichtenstern found a tuberculous bacillemia. Other patients have a persistent fistula following nephrectomy or epididymectomy for tuberculosis. Even after several years such patients have positive blood cultures. However, when the fistula closes, the blood cultures become negative. Bacillemia indicates the presence of an active tuberculous focus. If this is followed by negative blood cultures, it means that the lesion has healed.

BRAHDY, Mount Vernon, N. Y.

THE GERSON-HERRMANNSDORFER-SAUERBRUCH DIET IN DIFFERENT FORMS OF TUBERCULOSIS IN CHILDREN. O. WIESE, Ztschr. f. Kinderh. **51**:119 (May) 1931.

Wiese used the Gerson-Herrmansdorfer-Sauerbruch diet in its exact form, confusion having arisen as to its value because investigators modified it in one way or another. The cases of forty-six children are reported who remained on this schedule from four months to one year. There was no convincing effect on skin tuberculosis, and in the most suitable cases of bone tuberculosis the patients refused to take it. The result was poor in pulmonary tuberculosis. The diet is not without danger, because of its content of phosphorus. Recognition depends on whether it offers more and in a shorter time than other diets, and this it does not do. Wiese's experience is in accord with the experience of other workers.

EMERSON, Boston.

THE CLINIC OF CONGENITAL SYPHILITIC DISEASE OF THE THYROID. I. M. CHAIUTIN and I. A. GOLDENBERG, Sov. Vest. dermat. **9**:402 (April) 1931.

In two cases of congenital syphilis of the thyroid and the larynx, antisyphilitic treatment gave a good therapeutic result.

BLOOM, New York [ARCH. DERMAT. & SYPH.].

A STATISTICAL STUDY OF TUBERCULOUS MENINGITIS IN CHILDREN. F. MATSUDA, J. Pediat. (Tokyo), July 20, 1931, no. 374, p. 970.

Forty-five cases of tuberculous meningitis were analyzed on the pediatric service of the Nagasaki College of Medicine. The average annual incidence of the disease was 3.46 cases. Of all the cases of meningitis observed, a total of 107 cases, 51 were diagnosed as epidemic meningitis and 45 (42 per cent) as tuberculous. As to the age incidence, 73.3 per cent occurred in children under 5 years of age, of which 28.8 per cent were in infants under 2 years. The number of boys showed a tendency to predominate over that of girls. The seasonal incidence was as follows: July, 20 per cent; March, April and November, 13.3

per cent, and December, no cases. In 33.3 per cent of the cases there was a history of tuberculosis in the family, more frequently on the father's side. The course of the disease was between eleven and twenty-five days (75.6 per cent), the average being nineteen and one-tenth days. Of the total number, 37 patients died in the hospital, 8 were discharged unimproved and none recovered. A positive Pirquet reaction was seen in 71 per cent. In the blood, the most significant finding was neutrophilia, with a decrease in lymphocytes and eosinophils. The spinal fluid showed slight turbidity; xanthochromia was demonstrated in 31.7 per cent, pellicle formation was positive in 51.1 per cent, the specific gravity was increased in 57.1 per cent, and the pressure was between 260 and 350. Sugar either was decreased or had totally disappeared in 86.5 per cent. The globulin test was positive in all cases, and acid-fast bacilli were found in 48.3 per cent. As complications, tuberculosis in other organs of the body was demonstrated in 48.3 per cent of the cases.

KATO, Chicago.

BRONCHOSCOPIC TREATMENT FOR TUBERCULOSIS OF THE HILAR GLANDS. EELCO HUIZINGA, Nederl. tijdschr. v. geneesk. **75**:439 (Jan. 24) 1931.

Enlargement of the hilar glands, especially in young children, often gives rise to a stenosis of the bronchus or trachea and to its accompanying symptoms. The prognosis of these conditions depends chiefly on the succeeding lung disease. The cause of the enlargement may be tuberculosis. If, in this case, perforation of a tuberculous hilar gland into the lower airway has taken place, bronchoscopic removal of the caseous material or of the granulation formed at the place of perforation may prevent suffocation or the development of pulmonary complications. The author gives some examples of this bronchoscopic treatment.

VAN CREVELD, Amsterdam, Holland.

Internal Diseases

ACUTE MYELOGENOUS LEUKEMIA IN AN INFANT ONE YEAR AND EIGHT MONTHS OF AGE: CLINICAL AND POSTMORTEM REPORT OF CASE. J. HUBERT VON POURTALES, Arch. Pediat. **48**:463 (July) 1931.

The author reports a case of acute myelogenous leukemia occurring in an infant at the age of 1 year and 8 months. The report includes the results of physical examination, laboratory tests and autopsy.

WADDELL, University, Va.

PYELITIS IN CHILDREN. R. E. VAN DUZEN, Dallas M. J. **17**:93 (July) 1931.

The author states that pyelitis "is generally considered to include not only the true infections of the renal pelvis, but also any infection in the urinary tract" and that "pus in the voided urine except in female infants with vaginitis signifies pyelitis." He warns that cortical abscess or pyelonephritis often gives a pus-free urine, and that streptococcus and early staphylococcus infection may show no pus in the urine. Urine cultures are more reliable guides in this type of case.

Van Duzen recommends early cystoscopic examination with renal lavage in the severe cases before the child has time to become emaciated and dehydrated, and he refutes the arguments used most often against this procedure. With an expert operator and suitable equipment, pyelitis in the male infant should be treated the same way.

The author cites a number of cases in detail and suggests the use of chloral hydrate and sodium bromide plus topical application of procaine hydrochloride rather than the employment of general anesthesia in a child so toxic.

He ascribes the cause of death in these cases to (1) overwhelming sepsis, (2) acute exacerbation of an old nephritis and (3) cardiorenal failure.

SMITH, Dallas, Texas.

PYURIAS IN INFANCY. OCTAVIO DA VEIGA, Arch. de pediat., Rio de Janeiro **2**:104 (Feb.) 1931.

Owing to the difficulty of locating the anatomic lesion, the term "pyuria" may be used to indicate the syndrome of purulent infections of the urinary tract. Most pyurias are secondary to an alimentary infection; the most common pathway is hematogenic or lymphatic. Seventy per cent of the cases are due to Bacillus coli with frequent streptococcus and staphylococcus associations; other causative organisms are the gonococcus, Koch's bacillus, Eberth's bacillus and Oxyuris. Children from 6 months to 3 years of age are most liable to infection; other predisposing factors are lack of cleanliness in the child's care, constitutional disturbances such as an exudative diathesis, congenital malformations and other debilitating diseases, notably grip. The symptomatology varies greatly; it may suggest impaludism, tuberculosis, tracheobronchial adenopathy or nutritive disturbances.

The following therapeutic means have their advocates in selected cases: methenamine, methylthionine chloride U. S. P. (methylene blue), acriflavine hydrochloride, neoarsphenamine, alkaline therapy, acid therapy, proteinotherapy, hemotherapy with previous vaccination of the donor, pyotherapy and vaccinotherapy. The author favors a mixed treatment, either methenamine, phenyl salicylate or methylthionine chloride associated with autogenous vaccine therapy. Cataplasms or warm compresses over the bladder or vesicular lavages are indicated in case of pain. As a last resort, in occasional cases, nephrotomy or neprectomy may be successfully performed.

OLIVER, Columbus, O.

THE INCREASE IN EMBOLISM IN RELATION TO INTRAVENOUS INJECTION. FRIEDRICH WAHLIG, Klin. Wchnschr. **9**:2110 (Nov. 8) 1930.

The author considers the increase in embolism and thrombosis after the World War and during the last five years following the inflation. He lists the proved cases of embolism on the surgical service in patients who received intravenous injections between 1919 and 1928, and suggests that overnutrition following a period of undernutrition leads to a relative increase in embolism and thrombosis.

SILVERMAN, Syracuse, N. Y.

COPPER IN THE ANEMIA OF NURSLINGS. E. SCHIFF, H. ELIASBERG and N. JOFFE, Klin. Wchnschr. **9**:2144 (Nov. 15) 1930.

This is a preliminary report. Four nurslings were given 20 drops of a 1 per cent solution of copper sulphate, or about 5 mg. daily. The authors feel that this drug has therapeutic value.

SILVERMAN, Syracuse, N. Y.

ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT FOR PNEUMONIA IN CHILDREN. J. DUKEN, Klin. Wchnschr. **9**:2195 (Nov. 22) 1930.

Eight cases are reported in which artificial pneumothorax was used. The author looks on this form of treatment as occasionally advisable in unilateral pneumonia, with or without an interlobar exudate, which runs a protracted course and which may involve the danger of bronchiectasis. When unilateral pneumonia is complicated by bronchitis of the other side, pneumothorax is contraindicated.

SILVERMAN, Syracuse, N. Y.

PNEUMOTHORAX THERAPY OF PNEUMONIA IN INFANTS. J. JAHR and R. NEUMANN, Klin. Wchnschr. **9**:2200 (Nov. 22) 1930.

These authors agree with Duken that in some cases of pneumonia pneumothorax appears to have therapeutic value and is seemingly without danger. They consider this method indicated in pneumonia with a protracted course or when complicated with interlobar pleurisy. They report five cases.

SILVERMAN, Syracuse, N. Y.

THE DISEASE PICTURE OF PURPURA FULMINANS. H. BRÜHL, Ztschr. f. Kinderh. **50**:547 (Feb.) 1931.

Three weeks after an infection in a healthy boy aged 2 years and 10 months, there developed the classific picture of Henoch's purpura fulminans, which was fatal in thirty-six hours. The morphologic examination of the blood did not reveal any noteworthy deviation, but there was a complete absence of fibrinogen, and a certain weakness of the fibrin ferment system; accordingly, the ability of the blood to coagulate was extinguished. The disease was not hemophilia, for the child showed no previous tendency to bleed, and did not come from a family of bleeders. Moreover, in hemophilia there is never seen a lack of fibrinogen, and this lack stands in the forefront in purpura fulminans. Afibrinogenemia as a hematogenous factor in the origin of disease is known in a congenital lack of fibrinogen, and in severe injuries to the liver, such as acute atrophy and tuberculosis. The lack of fibrinogen may be latent for years. Another factor is an injury to the vessels. In the case being reported, diphtheria antitoxin had been injected at the age of 14 days, and again eleven days before the onset of the hemorrhages. The assumption of an anaphylactic reaction is consistent with the time and course: swelling of the glands on the third day, pain in the joints and bones on the fifth day and hemorrhages into the skin on the tenth day. An exanthem and eosinophilia were lacking. The diminution of fibrinogen and injury to the vessels is known in experimental anaphylaxis. In serum sickness the coagulation time is rather shortened. This case, then, does not correspond to typical serum sickness, and resembles the anaphylactic reaction. Finally, the fact that there was fatty degeneration of the Kupffer cells fits in with the centrally placed injury to the liver in anaphylaxis.

EMERSON, Boston.

CLINICAL PICTURE AND PATHOGENESIS OF JUVENILE ACROCYANOSIS. A. KREINDLER and H. ELIAS, Ztschr. f. Kinderh. **50**:608 (Feb.) 1931.

Juvenile acrocyanosis is marked by disturbances of the hypophysis, the sexual glands and perhaps the parathyroids (acroparesthesias). The mild paresis of the muscles of the hand in severe cases is due to diminished irritability. Capillaroscopy shows a spastic atonic condition, with a slow, intermittent circulation, and dilatation of the venous limb and of the subpapillary plexus. By the plethysmograph, hardly any changes are seen in the reflexes which concern the great vessels, oculovascular reflex and vasomotor reflex, but where the capillaries are concerned, noteworthy changes occur. These observations are confirmed by the oscillometric method. The capillaries are but little stimulated by histamine. The irritability of the parasympathetic system of the blood vessels is normal, but the sympathetic system is hyperirritable. Hydrophilia of the tissues, studied by the method of Aldrich and McClure, is considerably increased. Juvenile acrocyanosis is caused by disturbances of the endocrine glands; a histamine-like substance may be an inner secretion of the skin, which becomes insufficient when the function of correlated endocrine glands is disturbed; the lack of this substance disturbs the axon reflexes of the small vessels, and hence acrocyanosis arises. Treatment is by means of gland extracts, diathermy and massage.

EMERSON, Boston.

CASE OF DIABETES MELLITUS IN A CHILD WITH RECOVERY. S. NAGANO, J. Pediat. (Tokyo), March 20, 1931, no. 370, p. 398.

The author observed a case of diabetes mellitus in a girl, 12 years of age, who had frequent urination with loss of weight two months after an attack of tonsillitis. Physical examination gave practically negative results except for emaciation (27.1 Kg.) and the disappearance of the knee jerk. Urinalysis showed: an acid reaction, specific gravity 1.038, reducing substance 6.4 per cent, acetone, diacetic acid and beta-oxybutyric acid with no albumin; microscopic observations were negative. The blood picture and Mantoux and Wassermann tests were nega-

tive. The diet prescribed consisted in 180 Gm. of bread, 380 cc. of milk, half of a pear, some vegetables, soup and a small amount of fish, to be divided into three meals a day. There was a moderate degree of thirst, and 100 cc. of water was allowed. Under this treatment the urinary sugar went down to 2.4 per cent, but owing to the extreme degree of emaciation, the diet was increased to milk 540 cc., three eggs, beef 50 Gm., fish 50 Gm., vegetables 100 Gm. and chicken broth 100 cc., to be divided into three meals. This ration gives 30.4 Gm. of carbohydrate, 80 Gm. of protein and 62 Gm. fat, making a caloric value of 41.2 per kilogram. Twenty-one units of insulin were given daily in three divided doses. Under this treatment, the increase in the blood sugar disappeared and the patient went home after one month. The child now goes to school daily, and the diet at home consists of 140 Gm. of bread, 540 cc. of milk, 300 Gm. of vegetables and 50 Gm. of fish, together with some eggs, peanuts and fruits, without any insulin. Urinalysis, conducted at frequent intervals, still gives negative results.

KATO, Chicago.

CHRONIC DUODENAL OBSTRUCTION IN INFANCY CAUSED BY PERIDUODENAL AND PERIPYLORIC MEMBRANES. E. S. FRANK, Acta pædiat. **10**:302 (March 15) 1931.

Seven cases of chronic duodenal obstruction are reported in infants, ranging in age from 7 weeks to 8½ months. The diagnosis is not difficult when vomiting commences immediately after birth, especially when there is bile in the vomitus. The characteristic tumor of hypertrophic stenosis of the pylorus is absent; the gastric peristaltic waves are noticeably more feeble. When symptoms commence at a later period, the diagnosis is considerably more difficult. Sometimes repeated roentgen studies are required. One of the patients did not vomit at all, but complained only of pain during and shortly after nursing. The author considers the obstructing membrane a developmental abnormality rather than an inflammatory product. The operative technic is very simple; it is essential, however, to operate promptly. Two patients in the series died, four recovered completely, and one was greatly improved but continued to have mild attacks of vomiting, apparently from incomplete removal of the obstruction.

MCINTOSH, New York.

CURDLED COW'S MILK AND PYLOROSPASM. U. GRÜNINGER, Acta pædiat. **10**:445 (June 30) 1931.

In fourteen cases of pylorospasm (the criteria for this diagnosis are not clearly stated) the author obtained satisfactory results by feeding whole cow's milk reenforced with sugar and treated with rennet in such a way that fine curds were formed. The preparation appeared to have a satisfactory effect on appetite, vomiting and gain in weight. Most of the patients were simultaneously treated with phenobarbital, atropine or both.

MCINTOSH, New York.

BLOOD CHANGES IN ACUTE RHEUMATIC DISEASES OF THE HEART DURING CHILDHOOD. Y. ÅKERRÉN, Acta pædiat. **10**:473 (June 10) 1931.

Sixteen children with rheumatic cardiac disease were studied over periods of several weeks each, with particular reference to the erythrocyte sedimentation rate. The author concludes that an elevated sedimentation rate is a valuable sign of rheumatic activity, regardless of whether the temperature is elevated or not. The interpretation is complicated (*a*) by the necessity for excluding other concurrent infections that might increase the rate and (*b*) by the fact that in the presence of cyanosis the rate falls to within normal limits no matter how active the rheumatic process. The author draws conservative conclusions and pleads for further study.

An increase in leukocytes and thrombocytes also suggests rheumatic activity regardless of the temperature curve. This phase of the work is less completely studied.

MCINTOSH, New York.

NIEMANN-PICK'S DISEASE. S. J. SCHAFERSTEIN, Acta pædiat. **10**:523 (June 10) 1931.

A case is described in which the symptoms began at 12 weeks of age. The diagnosis was definitely made at 5 months, and the patient died at 13 months of age. Autopsy was performed. The differential diagnosis from Gaucher's disease is discussed.

McINTOSH, New York.

A CASE OF CELIAC DISEASE. V. MIKULOWSKI, Acta pædiat. **10**:592 (June 30) 1931.

The author presents the clinical report of a case of celiac disease in a Polish boy observed for two and one-half years.

McINTOSH, New York.

MYOTONIA CONGENITA IN TWO SIBLINGS. K. MOË, Norsk mag. f. lægevidensk. **91**:1392 (Dec.) 1930.

Two cases of myotonia congenita in siblings, in a boy aged 5½ and a girl aged 1½ years, are described. They showed hypotonic paresis of the muscles of the lower extremities in the gluteal region with absence of tendon reflexes. The muscles had been deformed, weak and toneless since birth; in the early stages of childhood walking and standing were impossible, and movements in bed alone could be carried out. No progression of the disease was noted. The arms were not affected. The muscles of the neck and lips were somewhat atrophic. Sensibility was retained. Gradually the children learned to do a little walking and standing. The author differentially diagnoses this condition from the Werdnig-Hoffmann disease by the absence of atrophy in the lower extremities and of progression. However, other phenomena such as the familial involvement tend to support Wallgreen's conception of the identity of the two diseases.

HART, Greenwich, Conn. [ARCH. NEUROL. & PSYCHIAT.].

Nervous Diseases

THE MEASUREMENT OF THE PSYCHOTIC AGE. GEORGE GARDNER, Am. J. Psychiat. **10**:963 (May) 1931.

By paralleling the development of thought and behavior at age levels in infancy with the actions and thoughts of the insane suffering from psychoses with varying degrees of intensity, Gardner hopes to measure the extent of a psychosis on a chronologic developmental basis. An infant at the age of 3 months sleeps most of the time, has no bladder or bowel control and has no cognizance of the outside world. So, a simple schizophrenic patient who is motionless and incontinent and has no contact with others is assigned a psychotic age of 3 months. At 6 months, an infant tends to grimace and pick up mannerisms, to play by himself and to imitate the sounds of others; the hebephrenic person, with silliness, indifference and echolalia, is accordingly classified at a 6 month level. At the age of 1 year, a baby indulges in bouts of rage, in temper tantrums in which he may refuse to eat or in which he may stiffen. He likes to chatter and babble unintelligibly; the corresponding psychotic behavior is seen in the excitement and babbling of the catatonic patient, whose psychotic age is established as 12 months. As the child grows older, he learns to sulk, resents his parents' instructions, feels misunderstood and becomes self-centered. Translated into psychiatric language, this is the paranoid personality.

From this point of view, a psychosis is analagous to a developmental defect rather than to a clinical disease entity. Gardner considers several explanations

for this — innate defect, fixation in the course of psychic development and regression. The author believes that a defective sympathetic nervous system is inherited and is acted on by stimulating environmental factors.

DAVIDSON, Newark, N. J. [ARCH. NEUROL. & PSYCHIAT.]

SPECIAL DISABILITY IN SPELLING. SAMUEL T. ORTON, Bull. Neurol. Inst., New York **1**:159 (June) 1931.

Spelling defects, like other expressions of speech, are found in certain families in association with left-handedness and are considered to be the result of variation in the establishment of unilateral cerebral dominance. The author demonstrated that defects in reading are almost always associated with defects in spelling, although each may appear independently. These defects or confusions follow definite patterns which are caused by poorly formed associations and recall of the sight, sound and writing of the word. There is, for example, confusion resulting from reversals of orientation of a symbol whose mere form closely simulates that of another symbol such as B and D, F and T and Q and G. This type is called static reversal. Another type of reversal is called kinetic reversal. Here the fault lies in the direction of progress. Warm is spelled "wram," night "inght," etc.; errors in vowels are very common due to the fact that each symbol stands for a variety of sounds. These are but a few of the types of errors. The author also discusses methods of treatment. The article should be read as a whole by any one dealing with school problems.

BEVERLY, Chicago.

A METHOD OF VENTRICULOGRAPHY. EDWIN M. DEERY, Bull. Neurol. Inst., New York **1**:193 (June) 1931.

The authors insert needles in the ventricles on the two sides in exactly the same way in order to determine more accurately the difference in the position of the two lateral ventricles as well as the difference in the amount of fluid obtained from each. The needles are inserted 3 cm. from the midline and 7 cm. from the external occipital protuberance. This exactness of procedure also makes it possible to determine standards with which each case can be compared.

BEVERLY, Chicago.

SPINAL TUMORS IN CHILDHOOD. JOHN CRAIG and ALEXANDER MITCHELL, Arch. Dis. Childhood **6**:11 (Feb.) 1931.

Two cases of spinal cord tumor are reported. A boy, aged 8 years, had a spinal cholesteatoma at the junction of the cord and cauda equina. Removal of the tumor was followed by recovery.

A girl, aged 8 years, who had had symptoms of a cord tumor over a period of eighteen months, was operated on, and the cord was found to be thickened, red and very vascular at the level of the seventh and eighth dorsal vertebrae. A section of cord was removed which on section showed tuberculous granulation tissue, a tuberculoma. Following this decompression operation, the child recovered completely.

KELLY, Milwaukee.

REFLEX MOTILITY IN THE PRINCIPAL DISEASES OF INFANCY. GIUSEPPI GELLI, Clin. pediat. **13**:517 (July) 1931.

After reviewing and studying the modern conceptions concerning the formation of reflex phenomena and briefly discussing the more commonly known types of reflexes, the author describes the behavior of reflex motility in the more common diseases of infancy. To this study he adds a report of his experiences in 3,222 cases in children from 1 to 12 years of age.

SIGNORELLI, New Orleans.

THE PRACTICAL AND THEORETICAL SIGNIFICANCE OF THE PROTEIN DETERMINATIONS IN THE CEREBROSPINAL FLUID IN NEUROLOGIC CASES. H. DEMME, Arch. f. Psychiat. **92**:485, 1930.

The results of the determination of proteins by the Kafka method in 2,000 cases are reported. This method consists in first determining the amount of total proteins by the use of the Esbach reagent; only 0.6 cc. is used in this determination. The amount of globulin is determined first with the ammonium sulphate method, and then also with the Esbach solution. This is subtracted from the total protein, thus obtaining the amount of albumin. The so-called protein quotient is then determined by dividing the amount of globulin by that of albumin.

The cases studied represented different types of nervous and mental diseases, and Demme found significant deviations from the normal in a surprisingly high percentage. Some of the conclusions are as follows: 1. The method described is the most useful for practical purposes, because it is easy to perform and requires very small quantities of fluid. 2. The determination of the protein and the relationship between its different components, as well as with the other contents of the spinal fluid, is of great importance diagnostically. The following are only a few of its uses: It can be used in the differentiation of acute infections of the central nervous system, in the differentiation of meningitis from sympathetic meningitis, in the differential diagnosis of syphilitic disease of the central nervous system and in the evaluation of sequelae to injuries to the skull. 3. In a number of diseases in which other methods do not show any deviation from the normal, definite changes were found by this method (Parkinson's disease, chorea and others). 4. The method permits further insight into the nature of the cerebrospinal fluid.

MALAMUD, Iowa City [ARCH. NEUROL. & PSYCHIAT.].

OCCURRENCE OF ABORTIVE CASES OF PROGRESSIVE MUSCULAR DYSTROPHY IN FOUR GENERATIONS. G. PAMBOUKIS, Med. Klin. **27**:209 (Feb. 6) 1931.

The author gives the genealogy of a family for four generations. The members of the preceding generations showed a muscular disease that was suggestive of muscular dystrophy, but that did not come to full development. In the fourth generation a fully developed picture of muscular dystrophy was found in a girl 15 years of age. In all cases the onset of the disease was at the age of puberty. This suggests the possibility of an endocrine disorder.

ZENTAY, St. Louis.

ACUTE ASEPTIC MENINGITIS. OSCAR HERTZ, Monatschr. f. Kinderh. **50**:233 (July) 1931.

This is a report of three cases of meningitis showing many leukocytes in the spinal fluid, but negative cultures. The symptoms lasted for four days, ending in recovery. The author reports the cases as aseptic meningitis.

GERSTLEY, Chicago.

THE GENESIS OF HYDROMYELIA. GEORG SCHAETZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:1, 1930.

"Hydromyelia in relation to the spinal cord is in a certain sense the same as internal hydrocephalus is to the brain" (Kaufmann). In such cases the hydromyelia is nothing more nor less than a manifestation of a general dilatation of the cavities of the central nervous system.

Schaetz reports the case of an infant, about 5 months of age, in whom meningitis developed, followed by an internal hydrocephalus. At necropsy the latter condition was found, together with a hydromyelia of the entire spinal cord. The entire ventricular system was tremendously dilated, and the foramen of Monro measured about 2.3 cm. The cerebellum was flattened out and pushed away by the markedly

dilated fourth ventricle. The roof of the fourth ventricle was covered by a membrane composed of dura, arachnoid and a part of the choroid plexus. The cerebral convolutions were naturally much flattened out by the pressure. The callosum was very small. The spinal cord when cut longitudinally looked like a sac, with a large cavity running its entire length. The walls of the cord measured from 1.5 to 2 mm. in the cervical region, 0.75 cm. in the dorsal region and from 1 to 1.5 cm. in the lumbar region. The sac was divided into numerous chambers by septums running here and there; these chambers were in communication with one another; their size varied a good deal, being largest in the cervical and lumbar regions, and smallest in the dorsal. Schaetz counted twenty-four septums in all, dividing the cord into chambers by their direction, running from side to side of the cord.

The case consists, therefore, of a high grade of hydrocephalus, with dilatation of all the cerebral cavities, as well as the foramina of Magendie and Luschka. The entire process was caused by an old meningitis that was most pronounced about the cisterna magna. In addition, however, there was an accompanying hydromyelia, which was separated from the hydrocephalus by a partially compressed but macroscopically intact portion of cervical cord. Microscopically, this portion of the cord was found to be penetrated by a dilated and compressed central canal. This separation of the hydrocephalus and hydromyelia by an intact portion of the cervical cord is of great importance.

Schaetz states that there is evidence pointing to the conclusion that spinal fluid is formed not only by the choroid plexus but also by the ventricular ependyma and at the glial limiting membrane of the vessels. Dandy and Blackfan found an internal hydrocephalus developing, according to Schaetz, after plugging the aqueduct of Sylvius, despite the removal of both choroid plexuses. This seems to demonstrate that the ependymal cells of the ventricle can produce a spinal fluid in quantities too great to be absorbed readily. It will be recalled that the internal hydrocephalus and the hydromyelia cavities were separated by a short piece of compressed but otherwise normal cervical cord without hydromyelia, caused by compression of this part of the cord by the expanding cisterna magna, which insinuated itself down through the foramen magnum, and by compression of the upper cervical cord entirely obliterated the central canal and the subarachnoid space in this area. Schaetz believes that this is an exquisite natural experiment to demonstrate that the ependymal cells of the central canal of the spinal cord are capable of secreting spinal fluid. The hydromyelia could not have been an extension of the internal hydrocephalus, and must have been produced in this way. The case demonstrates also that the direction of flow of spinal fluid is from the periphery to the center, and that a dilatation of the central portion must result if the common outflow for brain and cord through the foramina of Magendie and Luschka is obstructed.

The formation of chambers in the spinal cord was probably formed in the areas in which the spinal nerves took their exit, forming an area of resistance to the fluid and producing a gliosis and the formation of septums in relation to the nerves.

ALPERS, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

A CASE OF CHOROID PLEXUS PSAMMOMA IN THE RIGHT LATERAL VENTRICLE. A. TCHERNYSCHEFF, M. KOPYLOW and K. TERIAN, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:713, 1930.

The case reported was that of a child, aged 10, who since the age of 3 years had complained of headache and failing vision. Examination revealed bitemporal hemianopia, with bilateral choked disk and secondary optic atrophy, mild evidences of adiadokokinesia in both arms, dysmetria and intention tremor, hyperactive reflexes everywhere and a bilateral Babinski sign. Roentgen examination of the head revealed a dense shadow in the right lateral ventricle, conforming roughly to the shape of the latter. A diagnosis of hematoma or psammoma was made

on the basis of the roentgenograms. Necropsy revealed a large tumor in the right lateral ventricle, extremely hard and grayish-red. It was 9.1 cm. long by 3.8 cm. thick by 5.1 cm. wide. The tumor had crossed the midline through the right foramen intraventriculare and had penetrated into the left lateral ventricle. Here it compressed the thalamus, the stria terminalis and the nucleus caudatus. On the right side it compressed the caudate and thalamus. There was marked hydrocephalus. Above, the tumor was adherent to the corpus callosum. It compressed the cortex, especially the occipital lobe. The tumor weighed 154 Gm., and histologically proved to be a psammoma.

Bruns showed that parasitic tumors are most common in the ventricles, and that true tumors are much rarer. Both forms are found chiefly in the fourth ventricle, less often in the third ventricle and least often of all in the lateral ventricles. True neoplasms of the ventricles are rare according to Bruns, and consist either of ependymal tumors or choroid plexus tumors. Cystic tumors, sarcomas and psammomas also occur. Davis and Cushing found only 6 tumors of the choroid plexus (papillomas) in 964 cases of brain tumor. McCarthy reported a cholesteatoma of the lateral ventricle, and Wätzold a perithelioma of the choroid plexus. Burmeister found a mixed tumor (chondrofibro-epithelioma) of the choroid plexus containing brain sand. Oberling found what he called a meningoblastoma in the choroid plexus, which was in part sarcomatous and in part angiomatous.

ALPERS, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

PSYCHIATRIC EXPERT TESTIMONY IN CASES OF CRIMINAL MINORS AND WITNESSES OF YOUTHFUL AGE. EDITORIAL, Ztschr. f. Kinderforsch. **38**:367 (May 7) 1931.

This is the first of a series of articles dealing with case histories and a discussion by authorities.

REICHLE, Cleveland.

Diseases of the Eye

A CASE OF BILATERAL HEMIANOPIA WITH CONSERVATION OF MACULAR VISION. J. PALLARÉS, Ann. d'ocul. **168**:45 (Jan.) 1931.

In the case of a youth, aged 16, seen by Pallarés, the diagnosis was bilateral hemianopia with preservation of macular vision, caused by an injury at birth from the use of forceps. The labor had lasted eighteen hours in spite of several attempts at instrumental delivery. The patient was born asphyxiated with an enormous epicranial hematoma and weighed 6,000 Gm. Visual acuity was improved by galvanization.

BERENS, New York [ARCH. NEUROL. & PSYCHIAT.]

TWO CASES OF CONGENITAL ANOMALIES OF THE LACRIMAL PASSAGES. J. CHARAMIS, Arch. d'opht. **48**:216 (March) 1931.

Charamis reports two cases in which there were supernumerary puncta and canaliculi. In the first case, each lower lid contained a second punctum symmetrically situated 1.5 mm. outside the primary punctum. Probing demonstrated that these puncta represented bifurcation of the canaliculus. This case is readily explained on an embryologic basis. The second case presented on both sides in symmetrical locations on the skin, 2.5 mm. from the internal canthus, round, fairly large, pyramidal elevations with openings into them, from which tears had been noted to escape. These ducts were shown by probing to be connected with the culdesac. Their explanation is much more difficult on an embryologic basis. They may be fistulas.

MARLOW, Syracuse, N. Y. [ARCH. OPHTH.]

LITTLE'S DISEASE COMPLICATED BY ACUTE POLIOMYELITIS. E. APERT, DUHEM and M. BAILLET, Bull. Soc. de pédiat. de Paris **29**:74 (Feb.) 1931.

A boy, 10 years old, who was afflicted with Little's disease since birth, developed muscular weakness as a result of acute anterior poliomyelitis. Previously he could walk with the typical spastic diplegic gait, but after the onset of the poliomyelitis he was unable to walk. Diathermy treatment was instituted three months after the acute condition had subsided. The child began to show some improvement.

BENJAMIN, Montreal, Canada.

ACUTE EPENDYMITIS. R. DEBRÉ, G. SEMELAIGNE and R. BROCA, Nourrisson **19**: 246 (July) 1931.

Acute ependymitis disease has received but little attention in medical literature. The authors have encountered five cases since 1925, and include three others in their report. It always begins during the first few weeks of life. The onset may be abrupt with high fever, but is often insidious. The infant stiffens out from time to time, the face becomes congested and localized or generalized convulsions may be present. The general condition continues to be good; the baby increases in weight, and fever may be absent. In two of the cases reported, the condition was discovered accidentally during routine examination. Physical examination may reveal only one sign of importance, a bulging fontanel. The fundus shows no retinal hemorrhages. Lumbar puncture may give a normal spinal fluid. A positive diagnosis can be made only by securing some of the cerebrospinal fluid by ventricular puncture. The fluid thus obtained is always cloudy and contains polymorphonuclear leukocytes and pathogenic micro-organisms: pneumococci, Friedländer's bacilli and streptococci. The only efficacious treatment is repeated lumbar puncture. The disease is usually fatal. In most cases hydrocephalus develops before death. Two recoveries are reported. In one of the infants who recovered, vision was markedly impaired.

MCCLELLAND, Cleveland.

OPTIC NEUROMYELITIS. G. SALVATI, Arch. di ottal. **38**:310, 1931.

A new case of this somewhat rare condition is described. A girl aged 14 years was attacked by fever, pain in the joints and transient paralysis of the lower extremities and of the bladder, which subsided after two weeks. Five days after this, vision of the left eye was practically abolished; three days later the same condition occurred in the right eye. The globes were tender on pressure but not painful. A week later vision began to return in the left eye and five days afterward in the right eye. When the patient was seen by the author about two weeks later, vision was limited to counting fingers, with central scotomas inside of 20 degrees. The nerves showed postneuritic atrophy.

In comparing this case with about fifty similar ones in the literature, the only unusual observation is the occurrence of the symptoms of involvement of the cord preceding the visual disturbance, which usually occurs first. The course of neuritis is usually rapid, as in this case, proceeding to complete blindness of each eye in succession within one or two days after the first visual disturbance. Both eyes are usually involved, but a few unilateral cases have been reported. Vision has cleared up in many instances, often returning to normal. About 50 per cent of cases have terminated fatally. Postmortem observations in fifteen cases have shown an interstitial inflammation of the optic nerves and cord with degeneration of nerve fibers. The inflammatory processes in nerves and cord are separate, no inflammatory changes usually having been found in the brain itself. The cause is unknown, but apparently a common agent affects both nerves and cord. Treatment has apparently been without effect.

GIFFORD, Chicago [ARCH. OPHTH.]

VITAMIN THERAPY IN OPHTHALMOLOGY. SAL LENCE, Arch. de oftal. hispano.-am. **31**:386 (July) 1931.

The author considers xerophthalmia as due, in a great majority of cases, to avitaminosis. After extensive considerations of the present status of knowledge of the nature and mode of action of vitamins in normal cases and their therapeutic effect in cases of avitaminosis, and after reference to the best preparations in the market, the author considers that this medication is indicated in lymphatic keratitis, tuberculous keratitis and blepharitis in poorly nourished and debilitated children.

The author reports the case of a girl, aged 14, who had tuberculous antecedents. This patient had double tuberculous keratitis, with almost complete infiltration of the right cornea and loss of vision and less pronounced infiltration of the left cornea without appreciable vision, intense photophobia and marked circumcorneal injection. There were also macrocheilia and polyadenitis of the neck and submaxillary region, simulating adenoma. Under treatment with irradiated ergosterol, the polyadenitis disappeared entirely and the macrocheilia diminished; the right eye was not affected, but the left was improved, with disappearance of the photophobia and lacrimation. After some time the irradiated ergosterol was alternated with polyhormonal treatment. The author finally concludes that vitamins have a marked beneficial action on the ocular disturbances of infancy due to diathetic processes, tuberculosis not excepted; that with their use the duration of the processes is lessened and there is less likelihood of recurrence; that in phlyctenular keratitis their action is specific, and that their value as a reconstituent and regulator of altered metabolism is great.

FINLAY, Havana, Cuba [ARCH. OPHTH.]

THE ETIOLOGY OF TRACHOMA. MARIE FISCHER-ASCHER, Arch. f. Augenh. **104**: 441, 1931.

Cultures were taken from sixty patients with trachoma and from five children with well marked folliculosis, according to the technic of Noguchi for isolating Bacillus granulosis. The cases of trachoma were all typical. In eleven of the sixty cases B. granulosis was isolated, and of the isolated organisms transplants were successfully made from six for several generations. B. granulosis was never recovered from one case of folliculosis. Attempts to obtain satisfactory complement-fixation and agglutination tests were unsuccessful. Inoculations of nine Macacus monkeys with cultures received from the Rockefeller Institute were successful in only two cases in producing conjunctivitis with papillary hypertrophy. In one of these cases the uninoculated eye of the same animal contracted the disease. The conjunctival infection of these animals did not correspond with human trachoma in either its clinical picture or its course, but this does not disprove the etiologic significance of B. granulosis, for monkeys may not show the typical reaction of man to the bacillus, and also the particular stain employed may have lost some of its virulence.

ADLER, Philadelphia [ARCH. OPHTH.]

URANIN (SODIUM FLUORESCEIN) AS AN AID IN THE DIAGNOSIS OF MENINGITIS. J. C. SCHIPPERS, Jahrb. f. Kinderh. **132**:23 (June) 1931.

Twenty milligrams of uranin per kilogram are given in milk or cocoa two and a half hours before lumbar puncture. A concentration of 0.03×10^{-5} or more in the cerebrospinal fluid indicates meningitis. One exceptional case is reported. This test may throw light on the cause of certain types of hydrocephalus. In two cases of rachitic hydrocephalus the meninges proved impermeable.

CLAUSEN, Rochester, N. Y.

LOCALIZATION OF INTRA-OCULAR TUBERCULOSIS AND JUVENILE ANGIOPATHY. T. AXENFELD, Klin. Monatsbl. f. Augenh. **85**:465 (Oct.) 1930.

This paper has as its chief subject the group localization of hematogenous tuberculosis of the eye. Recurring phlyctenular scrofulous keratoconjunctivitis in Europe is doubtlessly connected with tuberculosis. The idea of its origin by pyogenic surface inoculation or by "exudative diathesis" may be refuted. "Eye scrofulosis" develops in the form of phlyctenae and allied corneal diseases only when the tuberculosis has invaded the bronchial glands. It is a process of allergy. Exogenous irritations and various bacteria may complicate the condition. The virus of tuberculosis is the deciding factor, even though this can hardly be demonstrated by culture, inoculation or staining methods. It would be a step backward, in Axenfeld's mind, if the connection between recurring phlyctenular keratoconjunctivitis and "scrofula," i. e., tuberculosis, was not duly considered. He points out, furthermore, that the destructive tuberculosis of other organs seems to be less frequent in those persons who have suffered from an early scrofulosis, and that they seem to be protected against actual intra-ocular tuberculosis. Intra-ocular tuberculosis is usually not found in patients with pulmonary or surgical tuberculosis, or in those afflicted with lupus, but in people who present no tuberculosis habitus. Tuberculin tests and roentgenograms of the thorax showed merely constant changes in the bronchial glands and an occasional involvement of the lungs. One group seems to exclude the other. On the other hand, miliary tuberculosis of the lungs is frequently complicated by the manifestation of miliary tubercles in the choroid. This fact rendered the diagnosis difficult until it became known that the larger number of all inflammations of the iris, the ciliary body and, also, the choroid and the adjoining sclera are of a tuberculous nature. Stock's experiments were available in clearing this question. He proved the susceptibility of the uvea to tubercle bacilli. Axenfeld admits that focal infection may occur, but by exact and continuous observation of persons with this type of uveitis, the tuberculous condition can usually be demonstrated.

Tuberculous retinitis was never observed by Stock and others; it is as rare as the formation of tubercles proper in the retina. Tuberculous diseases of the retina and the disk may lead to occlusion of the terminal retinal vessels and to extended necrosis.

Juvenile angiopathy, or tuberculous retinal phlebitis, however, is a typical retinal disease characterized by recurring hemorrhages. Axenfeld, in 1909, called it a hemorrhagic form of ocular tuberculosis. It seems to be identical with the "recurring hemorrhages in the vitreous" of young persons. The uvea is not involved at first. The tubercle bacilli do not get into the retina by way of the blood circulation, but in all probability enter the perivenous lymph sheaths after leaving the intact capillaries. This would suggest that tubercle bacilli may be in the tissues of the body without causing any disease. Axenfeld then compares this retinal periphlebitis with that of the brain.

STOLL, Cincinnati [ARCH. OPHTH.]

DYSTROPHIES OF THE CORNEAL PARENCHYMA. T. AXENFELD, Klin. Monatsbl. f. Augenh. **85**:493 (Oct.) 1930.

Axenfeld includes under the term dystrophies opacification of the parenchyma of the cornea occasioned by disturbances of its physiologic nutrition, but without any perceptible exogenous causes, i. e., injuries, inflammations or physiochemical lesions. Neither the so-called "trophic" changes due to disease of the trigeminus nerve nor the congenital, noninflammatory changes are considered in this paper.

Congenital and hereditary changes may be of consequence in the production of acquired dystrophies, such as keratoconus, which reduces the elastic resistance of the center of the cornea. The metabolism of the cornea is not very well known, nor is its ability to change the material supplied by the marginal vascularization, by osmosis and by diffusion from the anterior chamber. Changes of the stroma may

be endotheliogenous; i. e., "epithelial" dystrophies may be caused by an action emanating from the interior layers. Gerontoxon is caused by depositions of lipoids at a certain distance from the limbus because the tissues have lost their ability to change them, or because a larger quantity of lipoids is supplied by the marginal vessels than the cornea, under normal conditions, requires.

Axenfeld also refers to the influence of age on the development of gerontoxon, senile cataract and other changes in the eye. Hormonal therapy seems to be of no avail in senile cataract, although it may yield results in serious marginal degenerations of the cornea, such as chronic peripheral ectasia and peripheral groove formation. Adipose xanthomatous dystrophy belongs to this group. It is the result of cholesterol deposited in the form of anisotropal needle-shaped crystals. Groenouw's nodular dystrophy, the lattice-shaped form described by Haab and Dimmer and Fleischer's "hereditary type" are brought under the same caption as "nodular or latticed hereditary hyaline dystrophy of the cornea."

Calcareous dystrophy, or "calcinosis" of the cornea, is a slowly progressing primary calcification of the parenchyma, a rare form, first described by Axenfeld in 1917. Beginning near the limbus, it progresses toward the pupillary area, where minute dots can be seen with the slit-lamp. During eighteen years of observation, arteriosclerosis was never discovered. It is caused by diminished activity of the cornea.

Another form of dystrophy, bilateral symmetrical degeneration of the cornea with deposits of urea and sodium urate, was described by Uhthoff in 1915, and called uric dystrophy. In a patient, aged 53, a yellow opacity of the cornea, developing a short distance from the limbus, progressed toward the pupillary area. There were no signs of gout or uric diathesis. The elimination of urea was normal and was found in the blood under a diet containing little purine. A similar corneal condition was never met with in gouty patients, proving that the dystrophy in this case was brought on by conditions in the cornea.

Myxedematous, or mucinous, dystrophy, observed by Axenfeld in a boy aged 3 years, progressed for several years, forming white and prominent opacities in the center of both corneas. It developed into an opacity, in the shape of a butterfly, in one eye, while it finally covered almost the entire cornea of the other. Later, vascularization produced absorption, promising further restitution. The cornea showed fibrification of the lamellae and a positive mucinous fibrinoid reaction. The boy presented no symptoms of myxedema. Hormonal treatment, containing thyroidin, was of no avail.

Dystrophies of the cornea may present the same genesis, namely, a disease of the binding fluid (Kittsubstanz) between the lamellae, resulting in swelling and impregnation with various substances. The forms described are extraordinary, as they may develop at an at age that is usually no longer subjected to processes of "imbibition" in the body or in the vascular system. Referring to Windau's idea of excessive exposure to sunrays producing calcinosis in a man, Axenfeld suggested protection of the eyes against the light. He mentioned the case of a boy, aged 8, who was afflicted with calcareous dystrophy, and who was given goggles of dark Hallauer glass. They were set in an especially tightfitting, hard rubber frame, forming a permanently moist chamber, the eyes being, at the same time, protected against the ultraviolet rays. The calcareous deposits disappeared within a year to such an extent that the boy was again able to read. Saeger's galvanocautery applied from the limbus into the seat of the deposits may increase the resorptive process.

STOLL, Cincinnati [ARCH. OPHTH.].

TWO CASES OF TUMORS OF THE LIDS CAUSED BY FOREIGN BODIES AFTER OPERATION FOR ACUTE MASTOIDITIS. H. MITA, Klin. Monatsbl. f. Augenh. **86**:59 (Jan.) 1931.

Two school children, a boy aged 8 years, and a girl aged 7 years, had granugenol oil, a German proprietary form of a liquid petrolatum preparation, applied to their wounds after an operation for acute mastoiditis of the left ear. In the case

of the boy the left side of the face was swollen soon after the operation, leaving solid, hard tumors in the lids, lodged chiefly in the epidermis, and somewhat in the tarsus and in the orbital wall. These tumors persisted for over a year. The same phenomena were noticed in the girl about a week after the operation. The orbits, globes and their motion were not involved in either case, nor were the preauricular glands palpable. An attempt completely to shell out the tumors failed. The palpebral fissures remained narrowed. Histologic examination showed proliferating endothelial cells, partly in the process of necrosing or of transformation into connective tissue. Polymorphonuclear giant cells of various size were scattered all over. A portion of the connective tissue presented fibromatous structure; numerous round alveolae resembling fat cells were in evidence. The foreign matter producing the tumors was an oily substance which, in the author's opinion, may have been carried from the field of operation to their present location by way of the perivascular lymph spaces. The histologic picture reminded Mita of the granulomas observed in the neighborhood of the root of the nose after injections of paraffin for cosmetic purposes. Granugenol does not contain pure paraffin. No similar adverse results have been published.

STOLL, Cincinnati [ARCH. OPHTH.]

TABES DORSALIS IN CONGENITAL SYPHILIS. M. NONNE, München. med. Wchnschr. **78**:632 (April 10) 1931.

Nonne reports two cases of congenital syphilis with tabes dorsalis. This is an infrequent combination. In one case Wassermann tests of the blood and spinal fluid on several occasions were negative. The second case was one of congenital syphilis in the third generation. An examination of the spinal fluid when the patient was 8 years of age showed a three plus Wassermann reaction and a paretic colloidal gold curve. Seven years later there was no paralysis (only slight mental retardation) and the tabes had not increased. The tabetic symptoms were absent; the achilles and patellar reflexes were obtained and there was a diminished sensation of pain in both feet. Nonne warns against making a poor prognosis on the basis of the reaction of the spinal fluid, and emphasizes the slow and benign course of tabes in congenital syphilis. Crises, joint manifestations and ataxia are usually absent.

BRAHDY, Mount Vernon, N. Y.

Diseases of the Ear, Nose and Throat

THE ORGANIZATION OF SOCIAL SERVICE FOR SCHOOL CHILDREN SUFFERING FROM SPEECH DEFECTS. KARL C. ROTHE, Ztschr. f. Kinderforsch. **38**:39 (Feb. 3) 1931.

Any organization of this kind must be based on obligatory schooling, since neither the children nor the parents appreciate the importance of the treatment. At the present time, such classes are well organized in large cities, but not so well in small cities, and there are practically none in the country. It is extremely important to correct speech defects since they have a profound influence on the career of the child. The author offers a plan for the organization of these courses in Austria.

REICHLE, Cleveland.

SOUND TESTING OF STUTTERERS. O. VON ESSEN, Ztschr. f. Kinderforsch. **38**:53 (Feb. 3) 1931.

The author examined sixteen children in order to discover the frequency with which the various sounds were spoken defectively.

REICHLE, Cleveland.

Optical Intuition in the Deaf and Dumb. O. Schmaehl, Ztschr. f. Kinderforsch. **38**:67 (Feb. 3) 1931.

This research problem was instigated by the conception of the eidetic (E. R. Jaensch). This term is supposed to denote certain persons who are able to reproduce sensations with the reality that usually occurs only in the pathologic field of hallucinations. It has been determined that this capacity is found, as a rule, among youthful persons. The author considers it particularly interesting to find out how the deaf and dumb act in this respect. No such work has previously been undertaken because of the practical difficulties. He discovers that the methods for attacking this problem which were worked out by Jaensch suffice for the examination of the deaf and dumb; naturally, one must be acquainted with the peculiarities of this type of individual. The acme of the eidetic capacity is found to lie about the twelfth year. From then on it decreases in intensity; the only adults who had it were persons with artistic ability. Three types of eidetics were found: those in whom the intuitional phenomenon could be produced voluntarily; those in whom this was present only in a slight degree, and the third group to whom a picture or an object had to be presented before they could reproduce sensations. Deaf and dumb persons showing mental inferiority were found to possess this capacity to a greater degree than those of normal intelligence. However, their reproductions were, in contradistinction to those of the intelligent eidetics, uniformly inflexible. In other words, the author finds little difference between the normal children and the deaf and dumb in so far as the eidetic faculty is concerned.

Reichle, Cleveland.

The Influence of Speech Defects on the Learning Ability in the Elementary Classes. Hans Dirr, Ztschr. f. Kinderforsch. **38**:218 (March 12) 1931.

The author wishes to settle the problem as to the influence of different forms of speech defects on both the intelligence and the learning ability of children. It is true that children of poor intelligence almost always show poor speech and later poor ability to carry out any form of activity. However, a number of children whose intelligence appears to be normal are backward in their school work. This is undoubtedly due to the fact that hearing not only is necessary to learn to speak, but also plays a considerable rôle in the development of intelligence, much more so than, for instance, sight. It is therefore not astonishing that the experimental results of these investigations show that the learning abilities of speech-deficient children are always at about the level of their speech defect. Stammering that is due to functional reasons usually has a profound influence on the development of the child, whereas organic stammering due to some malformation of the mouth is usually not influential in this manner. Deaf and dumb children have never been satisfactorily examined, so that one does not know what their intelligence actually is. The agrammatical child usually awakens the impression of being mentally deficient. Stuttering, on the other hand, appears to have little influence on the intelligence or learning ability. As a general rule, the author offers the following: The more severe the defect in speech, the lower will be the learning ability. He also believes that it is wrong to have children of different learning capacities and different speech defects put into the same school classes.

Reichle, Cleveland.

The Tonsil Problem. W. Wolffheim, Ztschr. f. Laryng., Rhin. (Teil 1: Folia oto-laryng.) **20**:463 (May) 1931.

In the first part of the article Wolffheim discusses the physiologic significance, the function, of the tonsils. In spite of the numerous theories and the many experimental investigations this problem is still not definitely solved. As the most satisfactory explanation the author considers that theory which considers the

tonsils as well as the entire complex of the lympho-epithelial tissues, particularly up to the time of puberty, as the main site of the occult immunization of the body against infectious organisms that enter the respiratory and the digestive tract, and the secondary follicles are considered a protective mechanism against injurious bacterial action. In regard to the pathologic aspects of the tonsils, the author states that the pathologico-anatomic definition of tonsillitis is likewise not yet entirely clear. He then discusses the clinical aspects of acute and chronic diseases of the tonsils. It cannot be doubted, and it is proved by the results of operative therapy, that the tonsils may become sources of infection for certain organs as well as for the entire organism. The question when such foci are present in the tonsils and when they are the cause of an infection cannot always be definitely decided. The diagnosis in each case can be made only after the consideration of all the manifestations. The author thinks that tonsillectomy is advisable even if it is only probable that the tonsils are the source of the infection.

[Arch. Otolaryng.]

Congenital Absence of Sweat Glands and Ozena. O. Fleischmann, Ztschr. f. Laryng., Rhin. (Teil 1: Folia oto-laryng.) **20**:503 (May) 1931.

Fleischmann first lists the cases of congenital absence of sweat glands combined with deficiency of hair and teeth, which he found in the literature. According to some authorities these cases form a special clinical group showing an ectodermal defect of high degree, and they deserve special interest because the majority are combined with ozena. The relations of this disease to the malformation are as yet not fully explained. For this reason the author gives a detailed report of a case from his own observation. A comparison with the other cases reveals that the manifestations on the part of the skin can all be traced to an inhibition in its development by which an embryonal condition is retained, and the anlage of the cutaneous appendages is more or less suppressed. It can also be demonstrated that the same explanation applies to the entire mucous membrane developing from the stomodeum, because here one likewise finds an embryonal condition in the inhibition of the development of glands and teeth. In ozena concurring with a defect of the sweat glands a defect of the nasal mucous membrane is the cause of the ozena. Even in ozena that occurs as an isolated condition the same defect, although perhaps less pronounced, is probably the cause. This is proved not only by a study of the genealogical trees but also by the concurrence with other homogeneous manifestations, and likewise by the occasional simultaneous existence of other defects, particularly of the so-called ozena skull. As causes of the ectodermal defects neither congenital syphilis nor endocrine disorders were demonstrable.

[Arch. Otolaryng.]

Surgery and Orthopedics

Osteo-Chondrosarcoma Enclosing the Left Kidney and Suprarenal Gland in a Girl Aged Fifteen Years. F. Parkes Weber, Brit. J. Child. Dis. **28**:136 (April-June) 1931.

A 15 year old girl had been in the hospital for subacute nephritis six months previously. On the second admission she complained of pain and swelling in the lower part of the left femur. A roentgenogram showed what appeared to be a neoplasm. Removal of the tumor was attempted, but the patient died shortly after the operation. At necropsy the left kidney and suprarenal gland were found to be enclosed in a thick, firm whitish layer of neoplastic material which proved to be osteochondrosarcoma, i. e., identical with the tissue in the tumor of the femur. The question as to which growth was primary remained undecided.

Langmann, New York.

FRACTURES OF THE SKULL IN CHILDREN. CECIL P. G. WAKELEY, Practitioner **127**:75 (July) 1931.

In general, signs of fracture of the skull in children have the characteristics of fractures in other locations, e. g., pain, swelling and, occasionally, deformity if depressed fracture has occurred. In addition the following conditions may be present: (*a*) Shock: The fracture usually produces unconsciousness from the onset. The duration is from eight to twelve hours. The skin is cold and moist; there is a fall in systolic pressure; the respiration rate is increased. (*b*) Concussion: This may result in addition to shock. Anatomically, the condition represents a certain amount of ecchymosis or bruising of the brain. The commonest symptoms in children are giddiness, headache and vomiting. When shock is present, the unconscious state is prolonged and may last three or four days. There is incontinence and the temperature remains subnormal. The return to consciousness may be followed by headache and nausea and sometimes by loss of memory. (*c*) Cerebral Laceration: The most characteristic sign is pyrexia, and if the motor area is involved muscular twitchings may be present. These signs do not generally appear until after the symptoms of shock have passed off. (*d*) Compression of the Brain: This usually results from hemorrhage inside the skull; in rare instances a depressed fracture may be the cause. The characteristic symptoms appear after the signs of shock begin to clear. The patient becomes drowsy and complains of headache; extreme restlessness is noted and there may be delirium. The respiration rate is increased and the pulse rate falls. Unless relieved by spinal puncture or decompression, coma and death may result. (*e*) Cerebral Edema: This may be described as a local congestion with swelling of the brain tissue. There also may be an associated serous effusion into the subarachnoid space.

As to the treatment, Wakeley stresses the point that conservative treatment in the majority of cases will suffice. Linear fractures of the vault require only treatment for the accompanying concussion. Morphine is absolutely contraindicated. Potassium bromide and chloral per rectum should be sufficient for the extreme irritability. Hypertonic salt solution intravenously or per rectum and a 25 per cent solution of magnesium sulphate per rectum are the most valuable aids in the treatment for head injuries. Lumbar puncture is of definite value. Cerebrospinal fluid should be withdrawn slowly every three hours. In all depressed fractures in children, the author states, an operation should be performed within a week of the injury as otherwise there is danger of epilepsy ensuing at a later date. Compound fractures of the vault of the skull always call for immediate treatment. In the latter case antitetanic serum should also be given. The author also suggests methenamine every four hours for several days after the operation. When this drug is given by mouth, the formaldehyde which appears in the cerebrospinal fluid may aid in aborting meningitis. Fractures of the base rarely require any operative intervention except possibly to relieve conditions causing increased intracranial pressure. The author urges the need of prolonged rest in all cases of fracture of the skull in children. He suggests a period of at least from four to six weeks. He feels that the prognosis is much more favorable in children than in adults with the exception of patients in the age group from birth to 2 years. The more favorable prognosis in children is due to the difference in the anatomy of the skull and blood vessels. In children the bones of the vault are very elastic, the dura mater is more adherent to the skull, thus limiting extradural hemorrhage and, finally, the meningeal vessels are relatively very elastic.

SAPPINGTON, San Francisco.

SARCOMA OF THE PROSTATE AT THE AGE OF EIGHT YEARS. ERIC LLOYD, Proc. Roy. Soc. Med. **24**:859 (May) 1931.

In a boy, aged 8 years, cystoscopic examination showed a large mass in the region of the prostate. Shortly after this examination overflow and incontinence

developed and the child had to be catheterized. A few days later he became unconscious and convulsions occurred. He recovered, and later suprapubic cystostomy was performed, a piece of tumor being removed for microscopic examination. It proved to be myosarcoma. This tumor of the prostate is rare.

WILLIAMSON, New Orleans.

TUBERCULOUS OSTEITIS OF LEFT FEMUR. ERIC LLOYD, Proc. Roy. Soc. Med. **24**:859 (May) 1931.

A case of tuberculous osteitis of the left femur was reported in a girl aged 5 years.

WILLIAMSON, New Orleans.

TREATMENT OF CONGENITAL DISLOCATION OF THE HIP WITHOUT PLASTER. M. ROEDERER, Bull. et mém. Soc. d. chirurgiens de Paris **22**:744 (Dec. 5) 1930.

For years Roederer has sought for some substitute for the plaster cast in treating congenital luxation. He devised an apparatus consisting of a celluloid belt, with a rotary articulation, which proved unsuccessful. After many attempts, he has given up the quest and returned to the plaster cast.

BIEKER, St. Petersburg, Fla.

OSTEOSYNTHESIS BY A SCREW PLATE FOR FRACTURE OF THE HUMERAL DIAPHYSIS IN A CHILD. D. DUPUY DE FRENELLE, Bull. et mém. Soc. d. chirurgiens de Paris **22**:763 (Dec. 5) 1930.

A case is reported of fracture of the humerus in a boy of 12 years. Reduction was difficult and prolonged. A plaster cast was applied, but this failed to maintain reduction; the arm below the cast became much swollen, and the child was in great pain. An open reduction was done, and a Lane plate screwed in. Rapid recovery with excellent function followed. The author does not believe that the use of plates interferes with bone growth in a child of this age.

BIEKER, St. Petersburg, Fla.

ABDOMINAL PAIN IN TYPHOID FEVER IN INFANTS. P. NOBÉCOURT, Progrès méd., May 16, 1931, p. 897.

The author draws attention to the syndrome of abdominal pain in typhoid fever. This, he says, is always indicative of intestinal perforation and demands immediate operation. He presents a case as an example.

SANFORD, Chicago.

Miscellaneous

BASIS FOR THE ORGANIZATION OF THE SCHOOL MEDICAL SERVICE. CARLOS A. BAMBAREN and ERNESTO EGO AGUIRRE, Bol. Inst. internac. am. de protec. a la infancia **4**:645 (April) 1931.

The following points should be included in the activities of the school medical service: the bioanthropologic study of the school child; the psychologic analysis of the pupil so as to determine the extent of his mental development and point out the course that should be given to his instruction; the determination of the pupil's character, so as to appreciate his temperamental peculiarities; the psychotechnical study of the scholar, so as to discover his professional vocation; the hygienic and prophylactic care of the child, the teacher and the school premises; the selection of the children with respect to physical culture; the selection of weak children who are to attend special schools; the medical and dental care of children, with its corresponding division of social service; the specialized sanitary instruction of pupils

and teachers with the object of popularizing hygienic facts, and the cooperation of medical and psychiatric doctors to secure the specialized teaching of mentally handicapped children.

To be enabled to fulfil such aims requires the aid of the social visitor, since the service would be incomplete without her. All should count on her cooperation within the plan of organization, which should be as broad and humane as possible.

It is urgent that countries that do not take care of their pupil's health to such an extent should organize their school medical service as an autonomous independent unit within the administrative department in charge of primary instruction.

AUTHORS' SUMMARY.

THE SCHOOL MEDICAL SERVICE IN SOME CITIES IN THE UNITED STATES. CLARA E. HAYES, Bol. Inst. internac. am. de protec. a la infancia **4**:659 (April) 1931.

The aim of the school medical service is to preserve the health of the sound child and prevent its contracting any defect, and to improve the conditions of the child who enters school with any physical handicap. Parents should endeavor to have such handicap corrected; the school doctor informs them of the nature of the child's defect, indicating the course to be followed in order to attain the correction or cure, and by so doing provides both parent and child with hygienic instruction.

There is no uniformity in the plans or methods of the medical inspection of schools in the United States. Some states require the annual examination of all children; others make it compulsory only for children in certain grades—first, fourth and seventh in some instances; still others provide only medical supervision for the children selected by the teacher or the nurse. The number of children under the care of each doctor and consequently the frequency of the inspection vary considerably in the different states.

Medical inspection is being introduced in the rural school by means of the county health departments. The American Child Health Association is studying the way to have all cities between 50,000 and 500,000 population adopt such inspection.

The school medical service is yet in its initial period, and still has many problems in store. The most urgent is perhaps the recognition of the true importance of child health by the school authorities, the doctors and the parents, which will insure a greater cooperation between the home and the school.

AUTHOR'S SUMMARY.

SANITARY EDUCATION IN CHILE. CORA MAYERS, Bol. Inst. internac. am. de protec. a la infancia **4**:686 (April) 1931.

Sanitary propaganda in Chile is directed toward the improvement of agents employed to popularize, by all possible means, the principles of hygiene. Some of these agents are: the sanitary doctors, who are chiefly responsible for the demonstration of hygiene (there are 126 sanitary doctors in the eighteen provinces); the health nurses, trained in the School of Nurses of the University of Chile; the primary teachers, 5,000 of whom followed a correspondence course on school hygiene organized by the Department of Sanitary Education; the National School of Hygiene, which maintains a sanitary extension course for a group of primary teachers selected by the General Direction of Education (the teachers organized Little Mothers' Clubs in several girls' schools); the midwives, who have attended the classes on infant hygiene dictated by the Department at the concentrations in Santiago, and the clergy, who have also aided, responding to the call of Mgr. Errazuriz, Archbishop of Santiago.

Daily articles on hygiene sent by the department to all newspapers in the country, thousands of leaflets, tracts and pamphlets, lectures, posters, films and an Exposition of Child Hygiene were some of the means employed, among which the correspondence courses obtained most satisfactory results.

AUTHOR'S SUMMARY.

CHILD HYGIENE AND INFANT MORTALITY. MARIA ANTONIETA DE CASTRO, Bol. Inst. internac. am. de protec. a la infancia **4**:695 (April) 1931.

In spite of all that is being done everywhere in favor of the child, thousands of children die before completing their first year of life. In Sao Paulo, Brazil, the infant mortality rate was 176.43 per thousand in 1925, and 160.23 per thousand in 1928, the decrease being contemporary with the organization of the Inspection of Sanitary Education, which carries out an efficient work through the Health Centers.

The causes of infant mortality are well known; the problem consists in finding a remedy. Child hygiene begins with the pregnant mother, hence the importance of prenatal care. Between 1925 and 1928, 15,677 prospective mothers were assisted; an investigation that was carried out showed that 515 mothers who had 2,767 deliveries were thus distributed as to the care received:

	Prenatal Care, Per Cent	No Prenatal Care, Per Cent
Stillbirths	1.8	19.1
Premature births	5.8	8.4
Normal deliveries	95.9	72.4

The instruction provided to the mothers is extensive; they are trained in child hygiene, either separately or in groups.

AUTHOR'S SUMMARY.

DEVELOPING JUVENILE COURTS. KATHRYN SELLERS, Bol. Inst. internac. am. de protec. a la infancia **4**:706 (April) 1931.

The courts should provide the means of carrying out a full and careful investigation of each case, so as to keep adequate records and statistics which may be employed in administration and research studies. To this end they should have a staff of properly trained investigators and probation officers. Every court should count on the cooperation of a medicopedagogic clinic for the mental and physical study of the child and its guidance.

As far as possible, the child's correction should take place in the home; its separation from the community and its sojourn in an institution should be as short as possible. All transactions should tend to keep or reestablish the family bonds; only as a final extreme resource should the child be placed definitely in a corrective institution.

In the probation plan, the public school, police and all social service agencies should cooperate.

AUTHOR'S SUMMARY.

SOCIAL SERVICE FOR CHILDREN: RECENT PROGRESS IN THE UNITED STATES. SOPHONISBA P. BRECKINRIDGE, Bol. Inst. internac. am. de protec. a la infancia **4**:717 (April) 1931.

The training of social service workers in the field of childhood should be founded on the principle that treatment is to be preceded by investigation and that the care of each child should be adapted to its individual needs as discovered by the investigation.

The curriculum should provide the special studies which include information material (legislation on family affairs, history of child welfare institutions, doctrines of political and industrial organization, physiologic and psychologic bases of human conduct) and working material (methods of social work in relation to investigations and means of obtaining cooperation of experts in similar branches of work; methods of treatment in institutions; selection and supervision of rearing and foster homes; children's guidance under probation; social problems and methods of statistical research). It would be desirable to have the schools of social service affiliated with universities.

The registration of individual cases is valuable, but everything that might identify the individual should be omitted, so as to maintain the confidential character of such registration.

There should be a study program for actual workers who wish to improve their methods, and another for those who have just begun to study. A training course like that for law or medicine should be provided. Such a program should not be considered too vast, in view of the variety, the complexity and the importance of the work to be performed.

AUTHOR'S SUMMARY.

THE INFLUENCE OF OCCUPATION ON THE PHYSICAL DEVELOPMENT OF STRONG AND WEAK YOUTHS. L. SCHMIDT-KEHL, Arch. f. Hyg. **105**:17 (Feb.) 1931.

In this study, occupations were classified in two groups, "stimulating" or "nonstimulating," according to the physical effort required to follow the occupation. For example, blacksmiths and gardeners were placed in the "stimulating" group, while shoemakers and merchants are placed in the "nonstimulating" group. The author studied 2,620 youths ranging in age from 14 to 18 years. There were no gross average differences in physical development between the youths choosing the "stimulating" occupations and those who chose the "nonstimulating" occupations. After three years, however, the differences were considerable. Those in the "stimulating" occupations were much better developed physically than those in the "nonstimulating" occupations. At the beginning of the study, also, the youths in each group were classified as "strong" and "weak." Over a period of three years the strong youths following the stimulating occupations developed better, proportionately, than the weak youths, the strong ones being apparently more influenced by a stimulus to development than the weak. On the contrary, in the nonstimulating occupations, the strong persons developed less well, proportionately, than the weak. This is explained by the fact that in the absence of external stimuli, development is determined only by endogenous stimuli, which appear to be stronger in underdeveloped persons than in those who have already approached the usual limit of development.

Congenitally strong constitutions are developed completely only when properly stimulated by environment. Bodily exercise, however important this may be for weak persons who fail to get the proper physical stimulus in their work, is just as important in strong persons in developing the latent possibilities of their physical make-up.

GLASER, Rochester, N. Y.

THE CAMPAIGN AGAINST RICKETS. R. HECKER, Gesundhfürs. f. d. Kindesalt. **6**:83 (April) 1931.

The city of Munich has undertaken an intensive campaign against rickets. In addition to the propaganda in newspapers, an attempt is being made to instruct the population through schools. Physicians and nurses are being taught through postgraduate courses. In the social service clinics and in the outpatient departments groups of children are being treated according to a definite plan. It is apparent from the description of this plan, however, that not only is an attempt being made to cure and treat rickets, but the parents are being taught to feed the children according to the ideas of modern nutritional science. In addition to cod liver oil, viosterol is being used. Another group of children are being treated with light. It is interesting to note that this entire work has been carried out from Dec. 1, 1929, until June 30, 1930, at the cost of only 20,000 marks.

REICHLE, Cleveland.

A COMPARISON OF THE VALUES OF VACATIONS IN THE MOUNTAINS AT BATHS AND ON THE SEASHORE. H. LANGER, Gesundhfürs. f. d. Kindesalt. **6**:104 (April) 1931.

The author maintains that his experience has shown him that children sent to the mountains gain at first more rapidly, but have a smaller permanent gain than those who have been sent to the seashore or to some bath.

REICHLE, Cleveland.

THE PRESERVATION OF THE MILK TEETH. J. KIENTOPF, Gesundfürs. f. d. Kindesalt. **6**:112 (April) 1931.

Breast-fed children have better teeth than artificially-fed children. The position of the child when drinking can influence the formation of the jaw. Thumb-sucking and the use of pacifiers can produce anomalies. Breast-feeding develops the muscles of the mouth and so is of great importance in developing the jaw. It is well to use as small a hole in the nipple of a bottle as possible in order to stimulate these muscles. The child should be given firm food without fluids at the same meal as early as possible in the second year, in order to teach him to chew. Sticky, sweet foods should be carefully washed out of the mouth after each meal. The first teeth should be kept clean with cotton and water. A tooth-brush is of value only after the molars have appeared. The tooth-brush should be small and soft, and should be carefully dried after each use.

REICHLE, Cleveland.

THE NECESSITY FOR HOSPITALIZATION OF CHILDREN WHO ARE TO BE SENT TO FOSTER HOMES. H. FINKELSTEIN, Gesundhfürs. f. d. Kindesalt. **6**:125 (April) 1931.

Finkelstein has found it difficult to hospitalize foster children because of the financial conditions of the city, and therefore in this article he calls attention to the great danger which ensues for the child and for the foster home when the child has not been properly examined and watched over for a long period of time in the hospital. He calls particular attention to the example of syphilis.

REICHLE, Cleveland.

THE PROBLEM OF BEGGING CHILDREN IN SOVIET RUSSIA. N. OSERETZKY, Ztschr. f. Kinderforsch. **38**:1 (Feb. 3) 1931.

This article is concerned with the very actual problem of large numbers of children who have taken up begging as a profession. It is well written and describes the history of this problem. It groups begging children into three classes: In the first class children who beg only occasionally are found, in the second the habitués and in the third the criminals. It is interesting to note that even among beggars there is strict specialization. The author enumerates fourteen different groups, such as those who beg in front of churches, in cemeteries or in railroad stations and those who simulate disease or deformity, etc. He describes the character of the children and discusses the causes of this condition.

REICHLE, Cleveland.

FUNDAMENTAL PRINCIPLES OF THE FORMATION OF NATURAL ORIENTATION IN CHILDREN OF PRESCHOOL AGE. Z. A. GALPEROWICH and V. A. GERTZENSHTEIN, Omat det i ozdop **3-4**:75, 1930.

The main factor in bringing up children is to acquaint them with the nation and its ways, and also with the harmony between people and nature in general. In this way the child will be able to resist superstition, religion and class difference. At a very early age a child notices different things about nature, but there must be an adult to teach him to understand nature. For instance, it is necessary to explain to the child that in spring all plants begin to grow under the influence of the sun; that every season of the year has its own specific attractions; that the weather is different and the people are engaged in different kinds of work or business.

KRUPINSKI, Chicago.

Society Transactions

PHILADELPHIA PEDIATRIC SOCIETY

Stated Meeting, Dec. 8, 1931

JOHN P. SCOTT, M.D., *President, in the Chair*

RECENT PROGRESS IN EXPERIMENTAL ANEMIA. Presented by DR. DAVID L. DRABKIN.

Anemia may be produced experimentally in many ways, among which are (1) a single bleeding of large amount, (2) a series of controlled bleedings, so that the hemoglobin is maintained at a definite low level, perhaps the counterpart clinically of anemia due to chronic hemorrhages, (3) production of experimental scurvy, (4) phenylhydrazine hydrochloride poisoning, (5) the restriction of the diet of a young, growing animal to raw whole cow's milk and (6) splenectomy in rats infested with the parasite Bartonella muris, or the production of Bacillus welchii infection in dogs.

Only the anemias of the first five groups have been studied carefully. Under the second group belongs the important method contributed by Whipple and Robscheit-Robbins. By their technic, the relative number of grams of hemoglobin that are produced by dogs under various dietary regimens may be determined. This method of investigation has been largely responsible for the introduction of liver therapy. Anemias that are produced experimentally by different methods are, as a rule, found to be amenable to different forms of treatment. For example, the only effective treatment for the anemia of scurvy is the feeding of a source of antiscorbutic vitamin. For the pediatrician, perhaps the so-called nutritional anemia of the young rat on an exclusive diet of raw cow's milk is of greatest present interest.

In the problem of experimental milk anemia, the following facts may be pointed out: 1. It had been known for many years that infants become anemic on an exclusive milk diet. 2. It has been established, also for many years, that milk is deficient in iron. 3. Milk anemia in rats, contrary to that in human beings, is a relatively "new disease." Before Hart's original publication about five years ago, investigators had found it very difficult to produce anemia in rats, unless the rats were kept on a milk diet for several generations. Now, however, there is no difficulty in producing severe anemia by simply feeding very young rats an exclusive diet of milk for a period of six weeks or less. 4. It may not be justifiable to consider milk anemia in rats a truly "nutritional" anemia. In Drabkin's experiments, the rats on a milk dietary were not only anemic, but were "stunted"—they were like marasmic children. In the later stages of anemia, the intake of food decreases and growth ceases, so there may be an element of starvation in this anemia. It must be remembered that milk is an unusual dietary for rats, even when one considers merely the large intake of fluid.

There still exists a difference of opinion as to the exact nature of the deficiency in a diet of milk. Hart, Elvehjem, Steenbock and others at the University of Wisconsin have offered a great deal of evidence in support of the opinion that both iron and copper are specific in the treatment for milk anemia. In this opinion they have been joined by Krauss, Underhill and recently by Nelson. Titus and Hughes, and Mitchell and Miller have found that manganese is also an effective supplement. The work of Beard and Myers is interpreted as supporting the proposition that iron is specific in milk anemia, while a host of other metals—titanium, vanadium, chromium, manganese, nickel, copper, zinc, germanium,

arsenic, selenium, rubidium and mercury (many of which have been reported to be effective in treatment for the anemias of man)—merely catalyze, but are not necessary for the reaction of, iron.

In his experiments, Drabkin had no difficulty in demonstrating that in this type of anemia both iron and copper are better than a small quantity of iron alone. On the other hand, he found that relief from the anemia could be accomplished by transferring the rats to a synthetic ration that was very low in copper. He has, furthermore, offered evidence in support of the opinion that rats with milk anemia can be treated effectively by being given a supplementary diet of milk with a small quantity of iron (insufficient in itself to cause a cure) and by being given various amino-acids and related substances, notably glutamic acid and arginine among twenty odd organic compounds thus far tested. The deficiency, whatever it was, could be supplied presumably either by inorganic factors, or by small quantities of inorganic plus organic substances.

In other types of experimental anemia, investigators have found that organic besides inorganic factors are necessary for the regeneration of hemoglobin. Whipple and Robscheit-Robbins have shown that the dog responds far better to whole liver than to liver ash or extract. Hirasawa, Matsuoka and his associates, and Okagawa and Tatsui have found tryptophan (which Drabkin showed to be fairly effective in milk anemia of rats) and methyltryptophan to be effective in relieving experimental phenylhydrazine anemia in the rabbit and dog. Fontes and Thivolle have claimed that tryptophan and histidine are necessary for the normal formation of hemoglobin. From the standpoint of the structure of hemoglobin, it is reasonable to suppose that both organic compounds and iron are necessary for its synthesis.

The importance of copper has received added support from a certain amount of *a priori* evidence. Livers of infants at birth as well as those of newly born animals have a higher copper content than have the livers of adults. Earlier, this had been shown to hold also for the iron content of livers, and has been related to the need of these elements for the formation of hemoglobin, during the period when their intake (on a milk diet) is low. It is interesting to note that for years orthodox Jews, when anemic, have been permitted to eat fresh hog liver as well as oysters (both "forbidden" articles). The iron content of hog liver is unusually high, while oysters have an abundant supply of copper. Cunningham, Cook and Spilles have published reports of experiments that indicate that the feeding of copper appears to cause the mobilization of iron from the liver and spleen, perhaps the first direct explanation of the modus operandi of copper in anemia. None of this evidence, however, need be taken to support the contention of the specificity of copper for the formation of hemoglobin.

Beard and Myers have used in some of their experiments an iron preparation furnished by Hart and considered "ineffective"; nevertheless, they found that milk supplemented by this iron alone was quite effective in curing their anemic rats. One of the main difficulties in settling the problem of the specificity of copper has been the lack of a reliable method of analysis for the small quantities of copper under consideration. Drabkin's analyses of large samples of his synthetic diet indicated that it contained less copper (per rat per day) than was present in an equivalent quantity of the milk that he used. The inability of Hart, Steenbock and Elvehjem to obtain results with glutamic acid cannot be accounted for by the possible contamination of Drabkin's preparation with copper. From five hundred to a thousand times the quantity of glutamic acid fed by him per rat per day contains too little copper for determination by the methods of analysis in present use. Further experiments are needed to account for the discrepant results of different workers in this field.

NUTRITIONAL ANEMIA: ITS PREVENTION AND TREATMENT. Presented by DR. HUGH JOSEPHS.

The mechanism of anemia in infancy was studied by trying to determine how far anemia is the result of failure on the part of the hematopoietic tissue to form

the elements of the blood and how far it is the result of an increased amount of destruction of these elements. In regard to formation, there are two functions to consider: (1) the formation of cells, and (2) the formation of hemoglobin. Hemoglobin may be deficient because the elements that go to make up the molecule are not available, or because there is a failure on the part of the body to synthesize the molecule, even though the elements are present. The cases studied comprised those in normal babies in the first few months of life, those in premature babies and cases of so-called secondary anemia occurring in the first two years of life.

In new-born babies it was found that accompanying the fall in hemoglobin there was a very low reticulocyte count, but usually no great increase in the total excretion of urobilin. This confirms the opinion of most recent observers that the fall in hemoglobin at this time of life is due to a lessening of the rate of the formation of blood rather than to an increase in that of the destruction of blood. The lessening of the rate of the formation of blood is physiologic, leading to an adjustment of the rates of formation and destruction at a lower level than is present at birth. The fall in hemoglobin and red cells continues to a point below that at which equilibrium is eventually adjusted. As hemoglobin falls to its lowest point (70 per cent), the reticulocytes rise and the hemoglobin returns to a slightly higher level, where it remains or slowly rises. This takes place during the second month of life. Iron administered during the early period of falling hemoglobin appears to have no influence on reticulocytes or on the fall of hemoglobin or of red cells.

In the premature baby the fall in hemoglobin is more rapid and prolonged, and the rise, if it occurs at all, takes place much later. There is a virtual disappearance in reticulocytes at first; then as the hemoglobin becomes lower there is a gradual rise, so that when the hemoglobin reaches about 50 per cent, the reticulocytes comprise from 3 to 4 per cent of the red cells. Iron given during the fall in hemoglobin has no demonstrable effect on the course of the hemoglobin or red cells or on the reticulocytes, but after the third month, administration of iron has been followed by a rise in reticulocytes, red cells and hemoglobin. The rate of the destruction of blood as measured by the excretion of urobilin plays little or no part in any of these changes. Evidently, there is failure of the hematopoietic tissue to react, which is more profound and prolonged than in the normal baby. This failure is seen in the sending out of immature red cells into the circulation. There seems to be no disturbance in the function of the formation of hemoglobin, as the cells are well stocked with hemoglobin, and the color index tends to be high. The hypoplasia of the blood-forming elements is only relative, and the hematopoietic tissue is apparently capable of maintaining an equilibrium with the blood-destroying factors at a lower level than the normal. This behavior is in contrast to that of the rare case of congenital aplasia in which the blood-forming tissue is incapable of carrying on this function at any level. Dr. Josephs has seen two such cases in which life could be maintained only by transfusions of blood, and in which frequent examinations failed to reveal a single reticulocyte.

The factor of infections in anemia is somewhat complicated. The condition in most of the cases studied was pneumonia. There is usually some increase in the rate of the destruction of blood, not enough for clinical evidence, but enough to be easily demonstrable by determination of urobilin in the stools, and to account for the often rapid fall in hemoglobin. The excretion of urobilin tends to fall rapidly toward normal as soon as the infection is over, but there are sometimes fluctuations that may have a bearing on the rapidity of recovery of the red cells and hemoglobin. Reticulocytes tend to be reduced during the course of pneumonia and to rise after the infection is over, but the rise is often not extensive, and apparently in such cases the increase in hematopoietic activity is not great enough to more than balance the rate of the destruction of blood. The anemia of pneumonia seems to be due largely to a failure of formation of hemoglobin, for the red cells do not fall to the same extent as the hemoglobin, and the color index tends to be low. After the pneumonia is over and the reticulocytes have risen, the red cells may rise more rapidly than the hemoglobin. Iron administered during convalescence

has a marked effect on the reticulocytes, and it is often only after giving it that the rate of formation of blood is sufficient to cause recovery. Iron, by itself, appears to have more effect on the red blood cells than on the hemoglobin; not infrequently the former will rise to normal or higher, while the rise in hemoglobin will lag, with a consequent fall in color index. In such cases the effect of copper is most striking. The effect of copper is on the formation of hemoglobin primarily, and its use in these cases is followed by a marked rise in color index.

Another possible effect of infection is in causing a loss of iron to the body. Dr. Josephs has observed a slight negative balance in two cases of anemia with rhinopharyngitis, and in one case of pneumonia the loss was considerable and might have led to a serious depletion of the reserve.

The effect of faulty diet on hemoglobin and red cells is undoubted, but the mechanism of the effect and the particular factor or factors that are responsible are not at all clear. While the excretion of urobilin is somewhat increased, the reticulocytes are not deficient as in infections, and the hematopoietic tissue apparently is capable of maintaining equilibrium with the destruction of the blood at a low level of hemoglobin. The very low color index in these cases renders it quite probable that the principal defect is in the formation of hemoglobin, but whether this defect is due to the absence of materials for the formation of hemoglobin or to a failure to synthesize hemoglobin is not clear.

Virtually nothing is known of the limit of available stores of iron in the human body or of the extent to which the iron in milk is capable of supplying material for the formation of hemoglobin. Huguonenq's work shows that premature babies have little iron to draw on to make up for the deficiencies of milk. In infections, it is possible that there may be some depletion of available stores, and that anemia due to lack of iron may result when a milk diet is persisted in. From available evidence, one may conclude that anemia due to a deficiency of iron probably occurs in premature babies beyond the first four or five months of age as long as milk is the sole article of diet, and that it may occur after severe infection, especially if prolonged. Otherwise its occurrence in the first two years of life is somewhat problematical and has not been proved. The effect of the administration of iron does not solve the question, as its principal effect is on the activity of the hematopoietic tissue and the red cells, rather than on the hemoglobin.

Modern methods of handling milk have apparently tended to cut down its iron content to a very low figure, about 0.7 mg. of iron per liter. If not more than from 10 to 20 per cent of the iron in milk is retained, the amount of iron available from the milk at the present time would be grossly inadequate for the needs of the infant, while the milk prepared under less refined conditions would come nearer meeting the demands for iron. Some dried milk is better in this regard. This problem deserves further study.

Pyrrol Ring: While it is theoretically possible that anemia may occur, the basis of which is in lack of this building store for hemoglobin, such anemia has not yet been demonstrated in infancy. In Dr. Josephs' work, the inclusion of vegetables and eggs in the diet did not influence the rate of recovery.

Vitamins: In one child admitted to the hospital with scurvy and severe anemia, administration of orange juice alone was followed by a marked increase in reticulocytes and a rapid rise in hemoglobin. In other cases, however, in which there had been a deficient use of antiscorbutic material but no signs of scurvy, orange juice had no such effect. None of the other cases studied had any bearing on avitaminosis as a factor in anemia.

Toxic Factor: Some pediatricians hold that there is some toxic factor in milk, probably fat, that causes increased destruction of blood. The excretion of urobilin was definitely increased in Josephs' nutritional cases, even in the absence of infection. During recovery the excretion of uroblin returned to normal, even when the exclusive milk diet was continued throughout the course of recovery.

Treatment with Iron and Copper: Treatment was mentioned in discussing the anemia of infection. When iron was given, there was usually a rapid rise in reticulocytes which reached its height in from the seventh to the tenth day. If

this rise did not occur, it usually meant that recovery would be delayed. Failure to obtain a rise in reticulocytes probably means a poorly functioning hematopoietic tissue and is one of the bases for the belief that the hematopoietic tissue functions inadequately in the early months of prematurity and during the course of many infections. Following the rise in reticulocytes there occurs a rise in the red cells. The hemoglobin tends to rise rapidly when it is low to begin with, but there is a tendency for the hemoglobin not to go much above 50 or 55 per cent, while the red cells are rising to or above normal. The color index consequently tends to remain at about 0.5 or 0.55 or even to fall to that level if there has been an earlier rise. Copper, on the other hand, appears to act on the synthesis of hemoglobin rather than on the formation of red cells, and the color index invariably rises when copper is given. Copper had no effect on the reticulocytes or on the excretion of urobilin, while the only effect of iron on the excretion of urobilin was occasionally a temporary increase. Iron in the form of ferric ammonium citrate was used, and the indications are that inorganic iron is far superior to iron in food for the rapid cure of patients with anemia, probably because of its stimulating effect.

DISCUSSION

DR. JOHN F. SINCLAIR: Following Dr. Josephs' report published in the AMERICAN JOURNAL OF THE DISEASES OF CHILDREN, September, 1931, p. 719, I tried to follow his practical suggestions. They coincided fairly closely with those in Dr. Lewis' paper, which appeared about the same time in *The Journal of the American Medical Association,* April 4, 1931, p. 1135. We have found that we could not use the amounts of copper that were suggested in these two papers without causing a great deal of vomiting. We began with 0.5 per cent of copper solution. Now we use 0.25 per cent solution in addition to the saccharated carbonate of iron, but even with this percentage there is more vomiting than is desirable.

DR. JOSEPH STOKES, JR.: I should like to ask either Dr. Drabkin or Dr. Josephs how closely the results with rats may be compared to the results with human infants in these investigations?

DR. JOHN P. SCOTT: Do you use iron ammonium citrate in preference to other forms of iron, or for convenience? Have you had any renal irritation following the use of copper in accustomed doses?

DR. THOMAS J. BUTLER: In the earlier transfusions of blood in typhoid, a preliminary typhoid vaccination was used on the donor. Would the use of iron and arsenic or copper have a tendency to raise the value of blood in the donor before ordinary transfusion?

DR. THOMAS FITZ-HUGH, JR.: I should like to ask Dr. Josephs if he has made any hematocrit and blood volume studies? One must consider the question of hydration or dehydration in these infants in relation to the hemoglobin readings. Apparently from Dr. Josephs' study in infants, there is a difference in response to therapy as contrasted with adults. If I read Dr. Josephs' figures correctly, I would say that the reticulocyte crisis in his cases is synchronous with an already inaugurated rise in red cells and hemoglobin, whereas in our experience with adults it is almost another week after the reticulocyte crisis before a clearly significant change in red cells and hemoglobin occurs. I notice that when he feels that hemoglobin has ceased to rise after a period of from three to five days he considers this a satisfactory control period, and is willing to assume that the improvement that follows the addition of copper is due to copper. Our own experience, chiefly with adults, indicates that changes in hemoglobin and red cells may rise by steps; a period of four or five days or a week with nearly stationary count is not very infrequent, and then there is another rise without any change in therapy. In other words, some of Dr. Josephs' curves suggest spontaneous recovery. I bring these points up for information, and not as criticism about a subject concerning which I know very little, i. e., anemias of infancy. Dr. Josephs' theory of the marrow hypoplasia states of the new-born infant is interesting to me. In the infants that I have had the opportunity to study there were from 5

to 10 per cent of reticulocytes at birth; this count rapidly fell to normal after from twenty-four to forty-eight hours of postnatal life. Can one say that the bone marrow is hypoplastic because no excess of reticulocytes is found in the peripheral blood? The bone marrow in relapse phases of pernicious anemia is hyperplastic and filled with young red cells which seem unable to mature, and yet there may be but 1 or 2 per cent or less of circulating reticulocytes. I should like to know whether Dr. Josephs has made any studies of bone marrow that showed the marrow to be hypoplastic, or whether because of the condition of the blood he assumes this as a working hypothesis?

DR. D. L. DRABKIN: We realize that a great many findings in the field of experimental anemia may or may not have a practical value. Not so many years ago, two distinct anemias were recognized, primary pernicious anemia, a hemolytic process, and secondary anemia, secondary to some other cause. No one guessed that pernicious anemia would prove to be amenable to nutritional treatment. The way in which the discovery was made is interesting. Whipple had tried liver and found it effective in the hemorrhagic type of anemia in dogs. It seemed odd for Minot to use liver-feeding in pernicious anemia, in human patients, but he tried it and found that it was excellent therapeusis. In various ways a great many things of practical value are begun in experiments.

I should hesitate to say that iron plus amino-acids will prove to have any practical value. Iron and copper presumably serve very well in some cases. Some investigators found that iron alone worked, and one investigator found that iron and copper were not as effective as a mixed dietary, such as lettuce added to the milk.

If glutamic acid should prove to be effective, and if one can get the same effect by feeding raw beefsteak, why give glutamic acid? Therapeutics ought to be highly practical. As shown in Dr. Josephs' charts, when the hemoglobin reached a level at which iron presumably ceased to act, why not give more iron instead of adding copper? It may very well be that by doubling the amount of iron an added response might have been produced. Some investigators have given unusually large doses of soluble iron preparations to adults, with very good results.

An infant or a child is far from an ideal experimental animal. Slight intercurrent infections and changes in the consumption of food during a period of treatment for anemia, with no exact criteria as to the effects of slight illness, make the evaluation of a particular form of therapy a hazardous matter. I should insist on the following instructions: Put the child on a diet of milk, cod liver oil and orange juice. Leave the child on this diet for some time and make determinations of hemoglobin, etc. Then, after "standardization" on this basal diet, continue the same dietary, with the addition of iron or of whatever hematopoietic agent the effect of which you are interested in determining. By using a basal diet, which itself is a poor "hemoglobin builder," one of the important variables, an uncontrolled, hospital dietary, is eliminated.

DR. HUGH JOSEPHS: Following the administration of copper, I have seen vomiting and diarrhea only in older children. I do not know what to do, except to reduce the dose. I have been trying out a quarter of a dose, and apparently this is effective. With the dose I have been using, 1 cc. of 0.5 per cent copper sulphate per kilogram of body weight, I have never seen vomiting or diarrhea in children under 2 years of age. The copper is given in milk, as it is better borne when given in milk than when given by itself.

With regard to the question of renal irritation: I have never seen any pathologic effect on urine, but the effect has not been followed carefully. I do not usually give copper for more than a week or ten days, unless the hemoglobin is around 20 or 30 per cent, and then for not more than three weeks. I have not taken into account hydration. It is possible that in some of the severe cases there may have been some variation in blood volume, but certainly not enough to account for the rise in hemoglobin. Speaking about the rise in reticulocytes, I think it does contrast with what one finds in adults. That is, the red cells begin to rise just as soon as the reticulocytes do. The hemoglobin usually begins to rise just as soon as

the reticulocytes reach their highest point. With regard to the bone marrow in infants in the early stage of life, I can say that I do not know that it is hypoplastic. I made a mistake in saying hypoplastic bone marrow when I do not have direct evidence. The very low reticulocyte count at a time of rapidly falling hemoglobin and red cells, without increased excretion of urobilin seems to me evidence that the formation of blood is at fault. The term "hypoplasia" has been used for want of a better term.

I have used iron ammonium citrate merely for convenience, for no other reason. I think any compound would do.

With regard to my right to draw conclusions from these cases, they were merely examples; they have not included all the work, and I have not attempted to draw conclusions from them alone. I published a statistical analysis of this group in the *Bulletin of the Johns Hopkins Hospital* for October, 1931, lately from an analysis of about forty cases. The period of treatment with iron alone varied from a few days to four weeks, and from these cases was constructed a curve indicating the average response of hemoglobin to iron alone. By this means the effect of copper could be shown. As a result of this work, I disagree with Dr. Drabkin's statement regarding the necessity for a basal diet. Infections are an unavoidable evil. The only method of circumventing them is to study a sufficient number of cases. Dr. Drabkin asked about giving extra doses of iron. That was done in three cases with no further rise, so I concluded that I was giving the maximum dose, and that a larger dose would not increase the rate of rise of hemoglobin.

In answer to Dr. Butler's question I do not know anything about arsenate, never having used it for infants. Inorganic iron disappears from the blood stream so rapidly that it probably would not be very effective.

DR. FITZ-HUGH: Do you know of any type of anemia that one can study in which the hemoglobin is fairly constant at a low level, and in which one can introduce your treatment and get your response?

DR. JOSEPHS: I do not know of any type of anemia in which a rise of hemoglobin may not occur at any time, except possibly the constitutional types with hemolysis or hypoplasia, in which any treatment is ineffective. I think that the only proper method of study is the statistical one, unless one has an unlimited supply of identical twins on which to experiment.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

JOHN CAFFEY, M.D., *Secretary*

Dec. 10, 1931

HERBERT H. WILCOX, M.D., *Chairman*

SPECIAL PEDIATRIC BEARINGS OF ENCEPHALOGRAPHY. DR. BRONSON CROTHERS (by invitation).

The accurate appraisal of children with disorders of the nervous system is of considerable interest. Every one recognizes that detailed neurologic study, appropriate enough in adult clinics, breaks down if applied to babies and young children. On the whole, the characteristic difficulties in children are likely to depend on trauma or infection. In either case the lesion is likely to be diffuse, involving more than one group of cells.

Under these circumstances it is frequently necessary to deal with cases on the basis of anatomic and physiologic residues, on which, of course, depend educational prognoses.

Encephalography, in properly selected cases, gives invaluable information. In about five hundred cases at the Children's Hospital my associates and I have gained information that, we believe, assists us in making increasingly adequate plans for medical treatment and for education, and we are also beginning to formulate opinions concerning the etiology of the chaotic condition known as "cerebral palsy."

Obviously encephalography is a severe procedure, but it definitely offers a chance to obtain precise and useful information. In cases of paralysis, of epilepsy and of mental defect this precision is peculiarly welcome, to the family as well as to the physician.

NEW TRENDS IN ENCEPHALOGRAPHY. DR. LEO M. DAVIDOFF and DR. CORNELIUS G. DYKE (by invitation).

We are presenting here a preliminary outline of a large problem, and have confined ourselves for the most part to a perfection of the technic of encephalography. We wish to emphasize the possibility of obtaining good encephalograms with much less air than is usually introduced, and thereby materially decreasing the discomfort of the patient both during and after the procedure. We have learned to judge the amount of air necessary in any given case by taking a film after 20 cc. of air has been introduced and immediately developing it. Inspection of this film shows whether the ventricular system is normal in size or dilated. If the ventricles are within normal limits, from 55 to 75 cc. of air is sufficient for excellent encephalograms.

Furthermore, we are convinced that stereoscopic roentgenograms from four sides with the head both vertical and horizontal are necessary for proper interpretation of encephalograms. We have followed this procedure for two years in more than 300 cases, and have been able to demonstrate that the practice of taking the films in only the vertical or the horizontal position alone may lead to erroneous interpretations. We have been able to prove that this relatively large number of exposures entails no danger to the patient.

There are a number of important points, such as the rate of absorption of the air, the measurements of the ventricles and the significance of the various anatomic structures demonstrable on the encephalograms, that we cannot discuss in detail during this short presentation, so that it was necessary for us to demonstrate some of these points briefly on the slides.

DISCUSSION OF PAPERS ON ENCEPHALOGRAPHY

DR. B. KRAMER: In Dr. Crothers' paper on encephalography, his attitude toward the procedure is rather apologetic. I think that the presentations of this evening would convince the most skeptical person that the procedure is not only valuable in neurologic diagnosis, particularly with children, but, as Dr. Davidoff has said, indispensable.

Twelve years have elapsed since Dandy introduced ventriculography and encephalography as an aid in the diagnosis of brain tumors and various types of hydrocephalus. Inspired by this work, Wideroe attempted to localize tumors of the spinal cord by this method and was surprised to find that he had also succeeded in visualizing the ventricles and the cortical subarachnoid spaces as well as the basal cisterns.

Independently, Bingel carried out similar studies in 1921. While the method of ventriculography has interested the neurosurgeon, it seems also to have attracted the attention of the pediatrician and neurologist, more particularly abroad, so that there are now at least two rather elaborate monographs in German, one by Eckstein and one by Kruse, in addition to articles in this country by Crothers, Fay, Dandy, Pancoast, Pendergrass and others.

The procedure has been severely criticized by some and enthusiastically endorsed by others. Dr. Crothers' presentation leaves little doubt that encephalography has a definite place in pediatric neurologic diagnosis. When properly carried out

in carefully selected cases, this method aids materially in the exact diagnosis of fixed lesions of the brain, and thereby provides a more rational basis for prognosis. By this method, gross lesions of the brain, including dilatations of the ventricles, unilateral or bilateral, localized or diffuse, may be clearly visualized. Cerebral defects and enlarged cortical sulci due to convolutional atrophy are usually filled in with cerebrospinal fluid, but when this fluid is replaced by air, the resulting picture is striking. When the defect of cerebral tissue is marked, the procedure may cause complete collapse of one side of the brain.

The pathologist has been able at times to demonstrate the changes in the brain in cases of encephalitis following mumps, measles, whooping cough and other infectious diseases, as well as in lead encephalopathy. It is, however, surprising to find that these changes may be so marked that they are demonstrable during life by encephalography.

Encephalography is a simple procedure when compared with ventriculography. Trephining of the skull is unnecessary, and the dangers accompanying the penetration of brain substance, which is necessary in order to enter the ventricles, are avoided. In this simplicity there are both advantages and danger. The advantages we have already referred to. The danger lies in the fact that the method may be used by those who underestimate its hazards in cases in which its use is contraindicated, or in which it can yield no additional information. Alarming symptoms often appear during the procedure. Shallow respiration is a frequent symptom. Bradycardia may be observed during the withdrawal of fluid, only to disappear when air is introduced. Symptoms of collapse may follow, and aseptic meningitis usually develops. Fortunately, these symptoms disappear without sequelae in from a few hours to a few days. Infants tolerate encephalography much better than do older children. The severity of the reaction depends on the experience and the technic of the observer.

Discussions regarding the relative merits of ventriculography and encephalography are beside the point, since each has its own sphere of usefulness. The ventriculogram usually visualizes the ventricles only, although a roentgenogram taken twenty-four hours later may show air in the basal cisterns and over the cortex. An encephalogram reveals the outline of the ventricles and in addition may show the basal cisterns and the cortical subarachnoid spaces. The failure to demonstrate air immediately in the ventricles after encephalography is not always due to obstruction, for a roentgenogram taken twenty-four hours afterward may show that the air has entered the ventricles. This should never be omitted.

The experience of my associates and me is limited to a study of forty-four children suffering from a variety of conditions, of whom fifty encephalograms and three ventriculograms were made. This series includes various types of amentia, also cases of brain tumor, encephalitis, unexplained convulsions, brain abscesses, epilepsy and meningitis. In brief, all of these except one case of epilepsy and three cases of unexplained convulsions showed changes either in the ventricles or in the cortical subarachnoid spaces. These patients had suffered from convulsions for only a short time, a fact that may serve to explain the absence of demonstrable changes in the brain. One patient with mongolism showed no changes in the encephalogram. Of nine children who gave definite histories of intracranial injury at birth, only two failed to show gross changes in the encephalogram. Of nine cases of meningococcus meningitis, six showed hydrocephalus; one of these had a block. The child recovered, and when seen one year later appeared normal mentally.

Air encephalography by the lumbar route has been recommended as a therapeutic procedure in selected cases. The replacement of even a small amount of cerebrospinal fluid with air often serves to visualize the ventricles in patients with meningococcus meningitis, thereby establishing the patency of the foramina and of the sylvian aqueduct. There is some evidence that this procedure prevents the development of adhesions and possibly the formation of cortical abscesses in meningococcus meningitis. The rapidity with which dilatation of the ventricles may develop in infants is illustrated by a case of tuberculous meningitis. The

child showed marked uniform dilatation of both ventricles, although the symptoms of meningitis were of only one week's duration. A considerable degree of ventricular dilatation occurring during an attack of meningitis in an infant is compatible with normal mental development.

From a review of the literature and consideration of our own experience, we feel that encephalography may be a valuable aid in diagnosis and prognosis in selected cases in pediatric neurology. Its use as a therapeutic procedure still rests on an inadequate foundation. The correct interpretation of roentgenograms requires a knowledge of the anatomy and the pathology of the brain and a careful correlation of clinical data with the roentgenologic findings. A more exact definition of what may be considered normal, particularly with respect to cortical and subtentorial markings, is needed. A careful correlation of antemortem encephalograms and postmortem and operative observations, as well as a systematic follow-up of patients who have been subjected to encephalography, should aid materially in the correct interpretation of the roentgenograms and in the establishment of their diagnostic and prognostic significance.

DR. C. A. ELSBERG: I have nothing further to say than that I have been both greatly interested and deeply impressed by the cases that Dr. Crothers has presented, and I have the greatest sympathy for and with him in his attitude that all children should be studied in this way.

One ought to get away from the idea of grouping a large number of children as presenting "mental retardation," etc. By a study of all these children in this way there will be a great advance in the understanding of so-called defective children.

I want to add that I have been watching with the greatest interest and enthusiasm the studies that Dr. Davidoff and Dr. Dyke have been making, of which they said little in the time allotted. I think that when they have finished the work that they are doing, it not only is going to advance the technic of the method in connection with normal anatomy, but will give some surprising new facts regarding the pathology of conditions that can be seen by roentgenology in children as well as in adults.

DR. BRONSON CROTHERS: Obviously encephalography is not a procedure to be used without definite indications, but it has great advantages. The group of children handicapped by fixed lesions is large and on the whole has been inadequately studied. "Bad heredity," syphilis and other factors have been overemphasized.

As far as can be seen, injury, infections of various sorts and such poisons as lead can produce almost identical anatomic defects and comparable physiologic disorders. In view of the importance of the subject, it seems worth while to emphasize that encephalography is one of the measures that can be used in arriving at an accurate appraisal of the anatomic defect.

DR. LEO M. DAVIDOFF: I want to emphasize again that there is really very little mystery about the putting of air into the brain. It is as simple as pulling air into a bottle that contains some semisolid substance and some fluid, in which by a shifting about of this combination of semisolid substance, fluid and air, the air rises to the top. Thus, by choosing the position of the head described, one can outline almost any structure in the brain that reaches the surface.

Book Reviews

Body Mechanics: Education and Practice. Report of the Subcommittee on Orthopedics and Body Mechanics of the White House Conference on Child Health and Protection, Robert B. Osgood, M.D., Chairman. Price, $1.50. Pp. 158. New York: Century Company, 1932.

This is a report of a searching investigation made for the White House Conference on Child Health and Protection into the relation of body mechanics and posture to the health and well-being of children.

Body mechanics is defined by the subcommittee that conducted the investigation as "the mechanical correlation of the various systems of the body with special reference to the skeletal, muscular, and visceral systems."

"There is positive evidence," the report says, "to prove that not less than two thirds of the young children of the United States exhibit faulty body mechanics," and that this condition is likely to continue into adult life. The evidence gathered shows that improvement in body mechanics is associated with improvement in health and efficiency.

An important distinction is made in the report between training in the principles of good body mechanics and training in various physical exercises. The detailed recommendations and the suggested program of corrective exercises presented will be of value to all those concerned with the care and training of children.

The last half of the book consists of a study of "Posture and Physical Fitness" by Armin Klein, M.D., and of "School Children in Chelsea, Massachusetts" by Leah C. Thomas, of the Children's Bureau of the United States Department of Agriculture. These are most enlightening reports.

The whole volume calls attention to an important subject which must receive more recognition by the medical profession.

Diphtherieepidemien. By Dr. E. Friedberger. Price, 4 marks. Pp. 50. Berlin: Urban & Schwarzenberg, 1931.

The author believes that little can be said for the prophylactic use of diphtheria toxoids and diphtheria toxin-antitoxin, and he even questions the efficacy of diphtheria antitoxin therapy.

He mentions communities in America and elsewhere where toxin-antitoxin was not used and where there were decreases in morbidity rates comparable to those in other cities where prophylactic injections were generally employed.

His statistics only illustrate the point that diphtheria is a disease which waxes and wanes with the years. In places where there has been a natural lessening in disease incidence, it would be difficult to link decreased morbidity with an increased use of prophylactic measures. However, one cannot conclude from this that the increased use of prophylactic measures has no effect on the morbidity rate of the disease.

It would seem that a case can be made for the American program of prophylactic injections on the basis of the results of active immunization, with the production of negative Schick reactions after injections, of biologic tests, by laboratory experiments on animals, and of our experiences in orphan asylums and other institutions. The author could have discussed these points just as thoroughly as the statistical epidemiology of the disease. Certainly, no clinician who has seen more than a few cases of diphtheria will accept his thoughts on diphtheria antitoxin.

Though the author's inferences are too sweeping, his facts stimulate thought, and for this reason the book should be read.

"Orthopädische Therapie in der Allgemeinpraxis" angeborene Deformitäten. By Dr. Hans Spitzy. Price, 7 marks. Pp. 115, with 49 illustrations. Leipzig: Georg Thieme, 1932.

Packed in the clearly printed 115 pages of this little brochure is found all the information required by the general practitioner for recognizing and treating congenital deformities. Starting with wry neck and passing through congenital elevation of the scapula, including dub hand, polydactylism and deformities of hip, knee and foot, the author gives brief descriptions of symptoms, backed by illustrative photographs of patients.

The last part of the treatise covers the congenital malformations of the spine, pseudarthroses, cartilaginous exostoses and the various spastic paralyses. Indications for operation and outlines of technic are given for deformities requiring surgical procedures, always with an admonition to use the trained surgeon for these purposes whenever possible. Coming from this master orthopedist, the instructions can be relied on and easily consulted by the busy practitioner when confronted by these deformities. It is a delightful book.

Diagnostik und Therapie der Kinderkrankheiten. By Prof. F. Lust. Seventh edition. Price, 10 marks. Pp. 542. Berlin: Urban & Schwarzenberg, 1932.

The field of diagnosis and therapy in the diseases and disturbances of infancy and childhood is covered by Professor Lust with remarkable thoroughness considering the brevity of the book.

In the latter part of the book is a rather complete discussion of drugs that are useful in pediatrics, with the dosages for the different age periods. Although the book would be unsatisfactory for complete investigation of any disease process, as a reference for the practicing pediatrician, it should prove of great value.

Les enfants tuberculeux. By D. Taillens. Price, 25 francs. Pp. 206. Paris: L'Expansion Scientifique Française, 1931.

This book is another of the series on infantile pathology published under the direction of Professors Nobécourt and Cruchet. The author is professor of pediatrics at the University of Lausanne. The book is interesting and well written. Infantile tuberculosis is taken up as to etiology, pathology, diagnosis, prognosis and treatment. He considers the triad of treatment to be rest, air and diet. Actinotherapy, therapeutics and pneumothorax are discussed. Under prophylaxis, he discusses the pro and con of B C G vaccination fairly, and admits that in rare instances it may not be without danger.

Notes on Infant Feeding. By G. B. Fleming. Cloth. Price, 2/6. Pp. 45. Glasgow: John Smith & Son, 1931.

This manual is compiled with the object of aiding students in the feeding of infants. It contains parts on breast feeding, artificial feeding and the modification of diet in disease. The discussion of conflicting views has been avoided, and the quantitative more than the qualitative is stressed. As it is written from the Scottish standpoint, which is quite correct locally, the book may not be so satisfactory from a general standpoint, such as the feeding of undiluted whole milk to infants and the use of a teaspoonful of orange juice twice a week to prevent scurvy.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Professor Taillens, Lausanne, Switzerland.
Secretary: Dr. P. Oltramare, rue Decandolle, Geneva, Switzerland.
Place: Geneva, Switzerland. Time: July 15, 1932.

International Pediatric Congress

President: Dr. George Frederic Still, 28 Queen Anne St., London, W. 1.
Place: London. Time: 1933.

NATIONAL

American Medical Association, Scientific Assembly, Section on Diseases of Children

Chairman: Dr. Jay I. Durand, 1305, 4th Ave., Seattle.
Secretary: Dr. Alfred A. Walker, Highland Plaza Apartments, Birmingham, Ala.
Place: New Orleans. Time: May 9-13, 1932.

American Academy of Pediatrics

President: Dr. John L. Morse, 319 Longwood Ave., Boston.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.
Place: New Orleans. Time: May 13-14, 1932.

American Child Health Association

President: Dr. Samuel McC. Hamill, 1822 Spruce St., Philadelphia.
Secretary: Dr. Philip Van Ingen, 125 E. 71st St., New York.

American Hospital Association, Section on Children's Hospitals

President: Dr. Thomas B. Cooley, 7815 E. Jefferson Ave., Detroit.
Secretary: Miss Bena M. Henderson, 721 N. 17th St., Milwaukee.
Place: Detroit. Time: September 12-16, 1932.

American Pediatric Society

President: Dr. Howard Childs Carpenter, 1805 Spruce St., Philadelphia.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid, St. Louis.
Place: Rochester, Minn. Time: May 26-28, 1932.

Association of American Teachers of the Diseases of Children

President: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.
Secretary: Dr. Oscar Reiss, 1930 Wilshire Blvd., Los Angeles.
Place New Orleans. Time: May 9-10, 1932.

Canadian Society for the Study of Diseases of Children

President: Dr. G. A. Campbell, 164 Metcalfe St., Ottawa, Ontario.
Secretary-Treasurer: Dr. L. P. MacHaffie, 162 Clemow Ave., Ottawa, Ontario.

SECTIONAL

Central States Pediatric Society

President: Dr. Frank C. Neff, 406 W. 34th St., Kansas City, Mo.
Secretary: Dr. A. H. Parmelee, 715 Lake St., Oak Park, Ill.
Place: Kansas City, Mo. Time: Fall, 1932.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. A. Howard Spohn, 925 West Georgia St., Vancouver, B. C.
Secretary: Dr. L. Howard Smith, 734 Medical Arts Bldg., Portland, Ore.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

Chairman: Dr. Horton Casparis, Vanderbilt University Hospital, Nashville, Tenn.
Secretary: Dr. Luther W. Holloway, 117 W. Duval St., Jacksonville, Fla.
Place: Birmingham, Ala. Time: November 16-18, 1932.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Thomas J. McElhenney, 1722, 2nd Ave., Bessemer.
Secretary-Treasurer: Dr. John W. Simpson, 1117 S. 22nd St., Birmingham.
Place: Mobile. Time: April 19-21, 1932.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Charles E. Boynton, 118 Forrest Ave., N. E., Atlanta.
Secretary-Treasurer: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. R. T. Lucas, Shreveport, La.
Secretary-Treasurer: Dr. Suzanne Schaeffer, Chailie Bldg., New Orleans.

MEDICAL SOCIETY OF STATE OF NEW YORK

Chairman: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester.
Secretary: Dr. Adolph G. G. De Sanctis, 12 E. 11th St., New York.
Place: Buffalo. Time: May, 1932.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. H. B. Hamilton, 434 Aquila Court Bldg., Omaha.
Secretary: Dr. George L. Clark, 1817 Vinton St., Omaha.
Place: As announced by committee. Time: Second Thursday of each month from October to June, inclusive, 6 p. m.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Yates W. Faison, 121 W. 7th St., Charlotte.
Secretary: Dr. E. K. McLean, 121 W. 7th St., Charlotte.
Place: Various children's hospitals. Time: Twice a year.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. C. E. Bradley, Medical Arts Bldg., Tulsa.
Secretary: Dr. G. H. Harrison, 1200 N. Walker St., Oklahoma City.
Place: Tulsa. Time: May 14, 1932.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. T. D. Dotterer, 1512 Marion, Columbia.
Secretary-Treasurer: Dr. Julian P. Price, 117 W. Cheves St., Florence.

TEXAS PEDIATRIC SOCIETY

President: Dr. J. H. Park, Jr., 3717 Main St., Houston.
Secretary-Treasurer: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. St. Geo. Grinnan, 925 W. Grace St., Richmond.
Secretary-Treasurer: Dr. J. B. Stone, 2042 Park Ave., Richmond.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. E. McClelland, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. P. G. Albrecht, 2009 Adelbert Rd., Cleveland.
Place: 2009 Adelbert Road. Time: Four meetings, from September to May.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. Gladys Boyd, 56 DeLisle St., Toronto.
Secretary: Dr. Lawrence Murray, 1870 Bloor St., W., Toronto.

Bronx Pediatric Society

President: Dr. Joseph Golomb, 496 E. 17th St., New York.
Secretary: Dr. E. Leonard Benjamin, 2229 Valentine Ave., New York.
Place: Concourse Plaza, 161st St. and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

Brooklyn Pediatric Society

President: Dr. Irwin Schiff, 658 Eastern Parkway, Brooklyn.
Secretary: Dr. Louis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Last Wednesday of each month, except June, July and August.

Central New York Pediatric Club

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Fourth Thursday of October, January and April.

Chicago Pediatric Society

President: Dr. Henry E. Irish, 432 S. Lincoln St., Chicago.
Secretary: Dr. Bert I. Beverly, 8 S. Michigan Ave., Chicago.
Place: City Club. Time: Third Tuesday of each month.

Dallas County Pediatric Society

President: Dr. Gordon B. McFarland, Medical Arts Bldg., Dallas, Texas.
Secretary: Dr. Harold T. Nesbit, Medical Arts Bldg., Dallas, Texas.
Place: Bradford Memorial Hospital. Time: 1 p. m., first and third Saturdays of each month.

Detroit Pediatric Society

President: Dr. Charles Wilson, 10 Peterboro St., Detroit.
Secretary: Dr. Joseph A. Johnston, Henry Ford Hospital, Detroit.
Place: Children's Hospital of Michigan. Time: No fixed date; approximately once a month.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: T. Bolling Gay, 384 Peachtree St., Atlanta.
Secretary: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.
Place: Academy of Medicine, 32 Howard St. Time: Second Thursday of each month from October to April, 8 p. m.

Memphis Pediatric Society

President: Dr. William R. Graves, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month.

Milwaukee Pediatric Society

President: Dr. G. H. Fellman, 231 W. Wisconsin Ave., Milwaukee.
Secretary: Dr. George F. Kelly, 161 W. Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New England Pediatric Society

President: Dr. Lewis Webb Hill, 319 Longwood Ave., Boston.
Secretary: Dr. Gerald Hoeffel, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Herbert B. Wilcox, 39 E. 75th St., New York.
Secretary: Dr. John Caffey, 50 Haven Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Pediatric Society

President: Dr. Edward B. Shaw, 384 Post St., San Francisco.
Secretary-Treasurer: Dr. Lloyd Hardgrave, 384 Post St., San Francisco.
Place: Various teaching schools. Time: Monthly.

Northwestern Pediatric Society

President: Dr. Samuel Amberg, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Alexander Stewart, 459 Lowry Medical Arts Bldg., St. Paul.

Philadelhia Pediatric Society

President: Dr. John P. Scott, 2040 Pine St., Philadelphia.
Secretary: Dr. John D. Donnelly, 115 Bryn Mawr Ave., Bala-Cynwyd, Pa.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to June, inclusive.

Pittsburgh Pediatric Society

President: Dr. David H. Boyd, 200, 9th St., Pittsburgh.
Secretary: Dr. Theodore O. Elterich, 724 Highland Bldg., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to April, inclusive.

Richmond Pediatric Society

President: Dr. John S. Weitzel, 3103 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. W. E. Chapin, 922 Floyd Ave., Richmond, Va.
Place: Retreat for the Sick, 2621 Grove Ave. Time: First Thursday of each month (other than during the summer).

Rochester Pediatric Society

President: Dr. S. W. Clausen, Strong Memorial Hospital, Rochester, N. Y.
Secretary: Dr. F. W. Bush, 221 S. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: First Friday of each month from October to May.

Rocky Mountain Pediatric Society

President: Dr. C. H. Platz, Fort Collins, Colo.
Secretary: Dr. R. H. Verploeg, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: Third Saturday of each month from September to May, inclusive, 2:30 p. m.

St. Louis Pediatric Society

President: Dr. Gustave Lippmann, 3720 Washington Blvd., St. Louis.
Secretary-Treasurer: Dr. Katherine Bain, 3720 Washington Blvd., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

Seattle Pediatric Society

President: Dr. C. L. Smith, 1215, 4th Ave., Seattle.
Secretary: Dr. N. W. Murphy, 515 Cobb Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, 7 p. m.

Southwestern Pediatric Society

President: Dr. William M. Happ, 523 W. 6th St., Los Angeles.
Secretary: Dr. Jeanette Harrison, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Henry G. Poncher, 5325 Kenmore Ave., Chicago.
Secretary: Dr. John P. Parsons, 320 S. Division St., Ann Arbor, Mich.
Place: Ann Arbor, Mich. Time: November, 1932.

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